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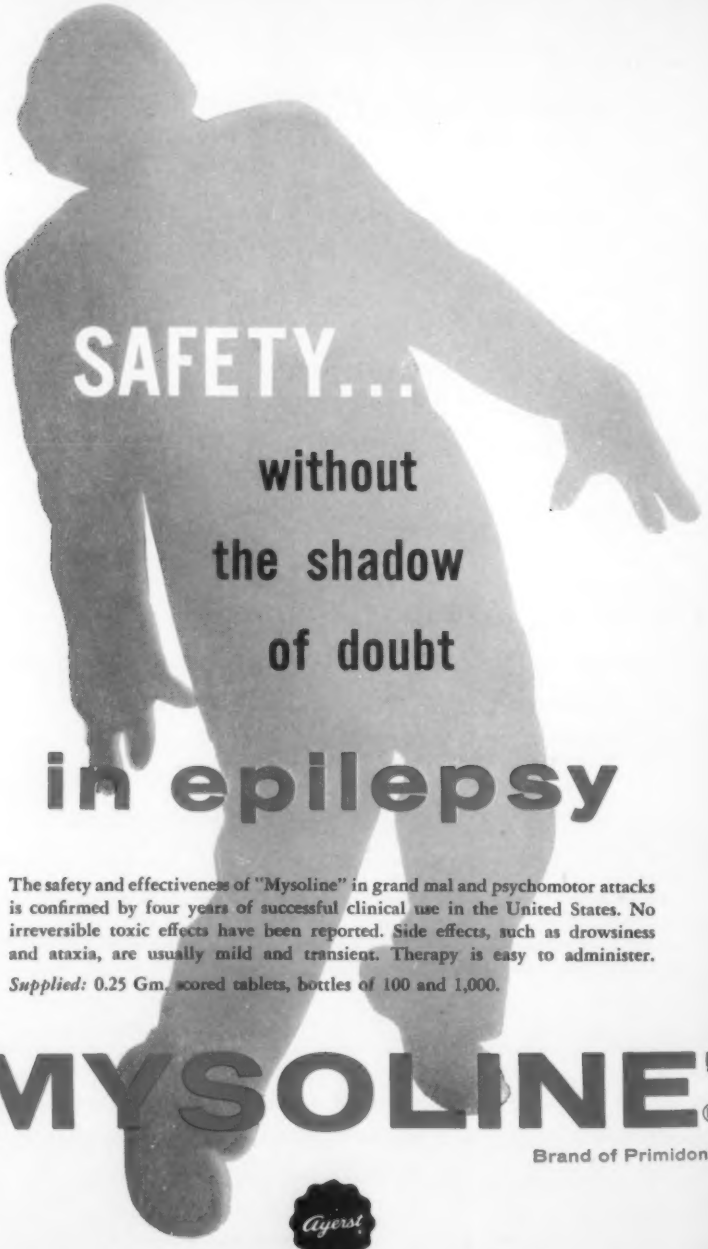

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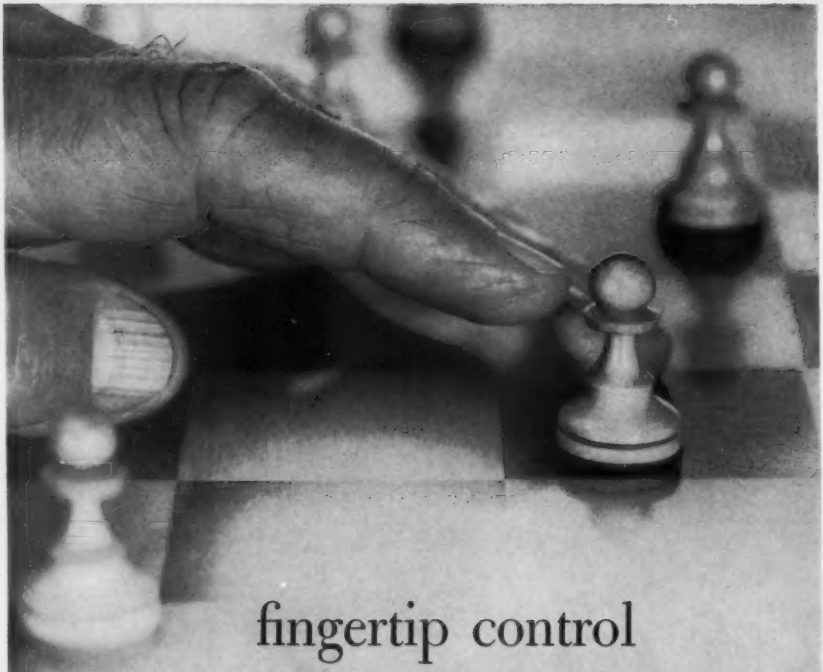

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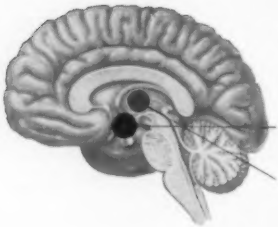

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2. Berger, F.M.: J. Pharmacol. & Exper. Therap. *112*:413-423 (Dec.) 1954.
3. Ehrmantraut, W., et al.: Presented as a Scientific Exhibit, District of Columbia Medical Society Convention, Nov. 24-26, 1958.
4. Parks, R.V.: Internat. Rec. M. *171*:678-683 (Nov.) 1958.
5. Case reports on file at Wyeth Laboratories.

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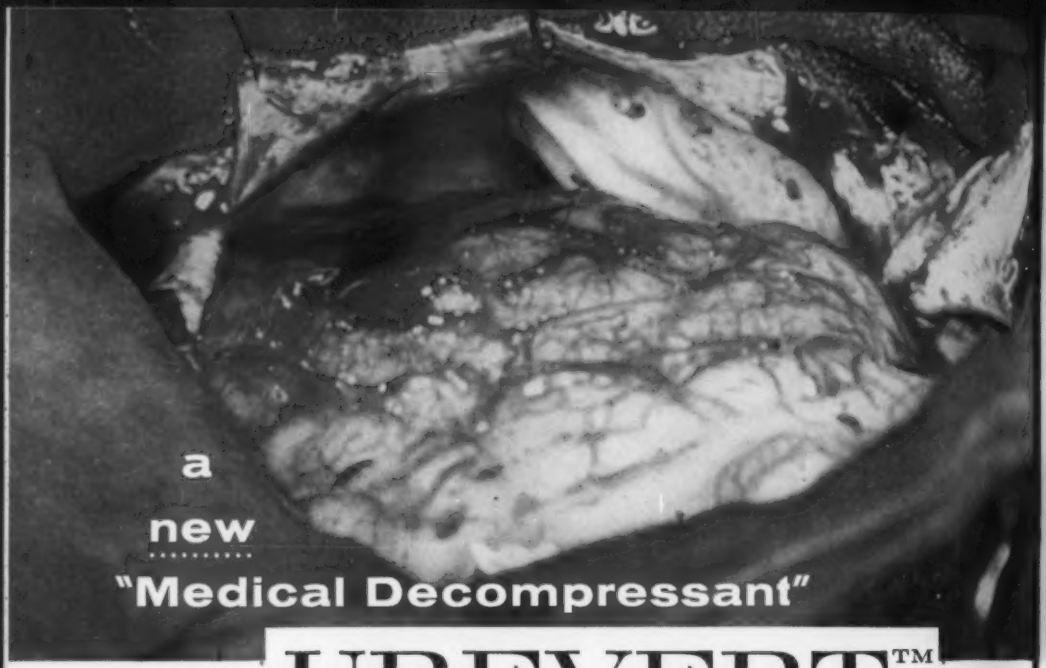

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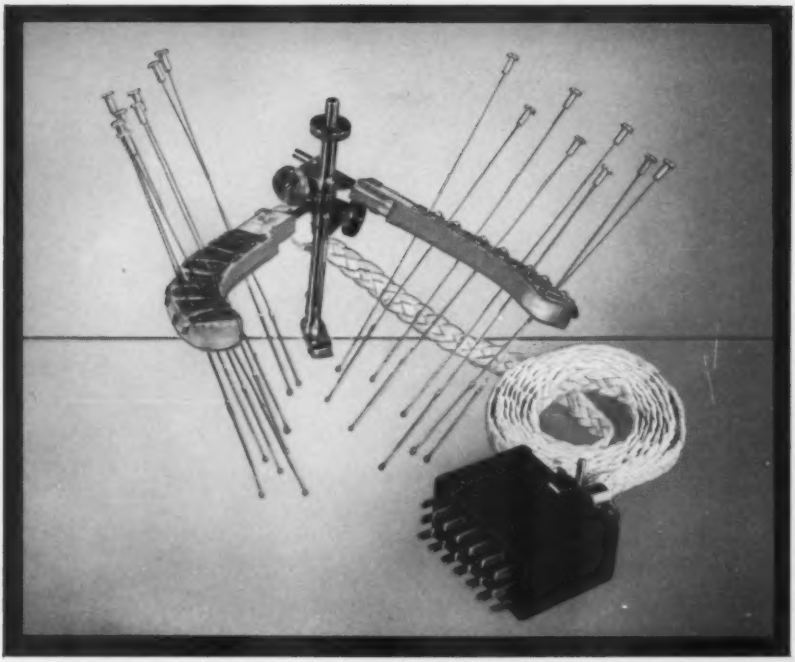

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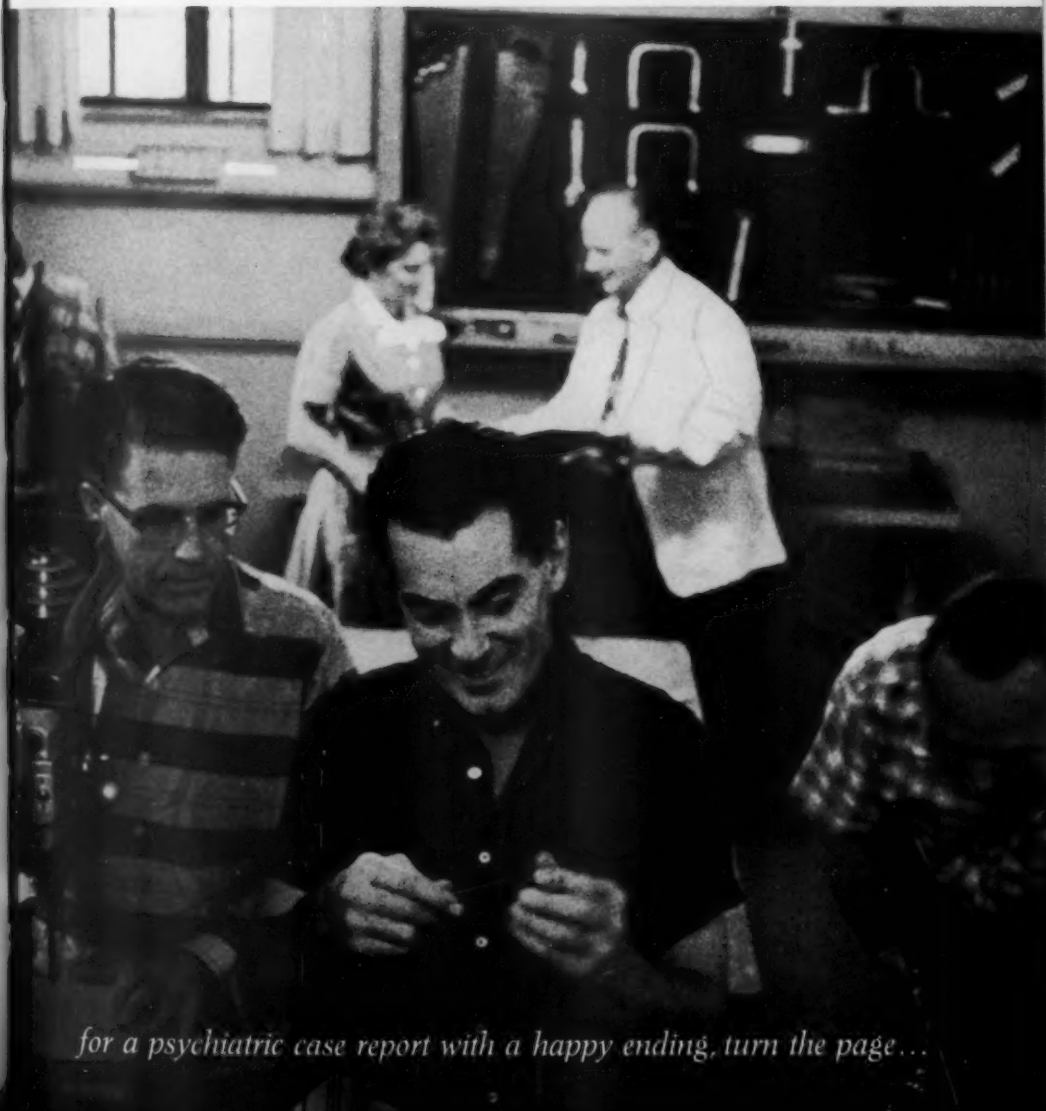

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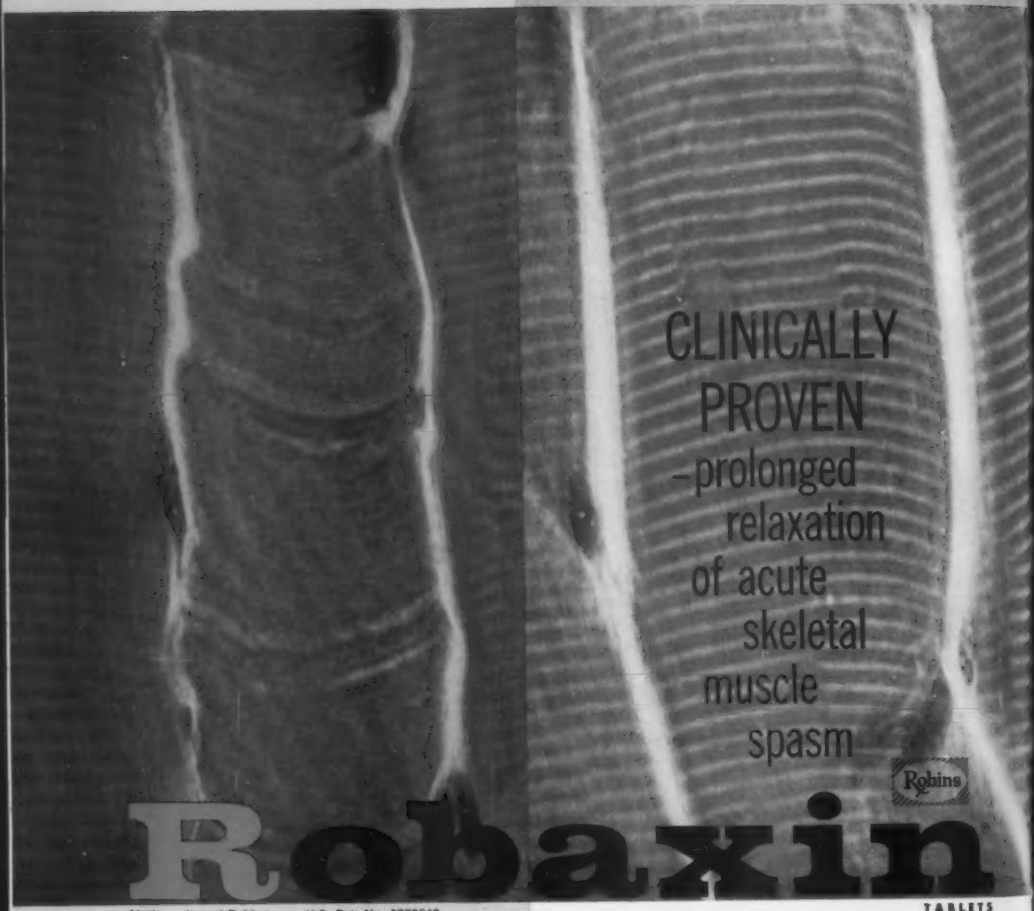

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Neurology Volume 9 • Number 4

Paroxysmal dysarthria and ataxia in multiple sclerosis

A report of 2 unusual cases

Frederick Andermann, M.D., James B. R. Cosgrove, M.D., Donald Lloyd-Smith, M.D., and Allan M. Walters, M.D.

THE PURPOSE OF THIS PAPER is to discuss 2 patients with multiple sclerosis who had numerous attacks of speech disturbance and ataxia. These attacks were sudden in onset and cessation and of brief duration. A search of the literature has failed to reveal descriptions of similar patients although many other speech disturbances and paroxysmal phenomena are described.

In 1868, Jean Martin Charcot[1] wrote: "Speech difficulties are almost constantly encountered in multiple sclerosis." He attached sufficient importance to this symptom to include it in his famous diagnostic triad. We owe to Charcot the description of the progressive nature of the articulation disorder known as scanning speech and its characteristic form in multiple sclerosis. He also mentioned that, in some patients, exacerbations of speech disturbances may be sudden and acute, followed by temporary remission. It has been accepted more recently that scanning speech is primarily a symptom of the advanced phase of the disease, and its early diagnostic value is limited. However, Ellerman,[2] and Brown and Putnam[3] have reported cases in which dysarthria was the earliest symptom. Oppenheim[4] mentioned, in addition, bradylalia, hoarseness, monotonous voice, and abrupt changes in register. Paresis and, rarely, paralysis of the vocal cords are reported by Lähr,[5] Lori,[6] and Leube.[7] Rethy[8] described a tremor of the vocal cords resulting in a tremulous phonation.

Scripture[9] undertook a study in which the speech of multiple sclerosis patients was recorded on a "phonautograph." After analysis of records, he attributed the peculiar vibrations, the irregularities of breathing, and the inaccuracy of enunciation to ataxia and the thickness of speech to spasticity of muscles of articulation. He thought staccato speech consisted of ataxia plus the forced effort of the patient to coordinate his breath control. Scripture's analysis of speech in multiple sclerosis revealed the following characteristics: slow speed and normal volume, alterations of rhythm, and diminution of stress and pitch. Breathing is

Drs. Andermann, Cosgrove, and Lloyd-Smith are from the Department of Neurology and Neurosurgery, McGill University and the Montreal Neurological Institute, Montreal, Quebec, Canada. Dr. Walters is from the Department of Medicine, University of Toronto and the Toronto General Hospital, Toronto, Ontario, Canada.

irregular as is laryngeal pitch control. Hence, sentence melody is lost, resulting in a monotonous voice.

Incidence of speech impairment in multiple sclerosis varies in reports from 10 to 50%.[10,11] Most series show an incidence of 10 to 20% of patients with scanning speech, although these series include patients in all stages of the disease. More unity of opinion is found concerning the prognosis of speech disorders. Ragnar Muller[10] reports in his series that the prognosis for dysarthria is very poor and that the disorder practically never recedes. A similar opinion is held by Paul Thygesen[11] who considers scanning speech indicative of multiple sclerosis of an advanced form and, as such, less prone to remission. An exceptional opinion is that of Lesny and Polacek[12] who report remission in half their cases of scanning speech. This is difficult to accept.

Cardinal features of attacks of dysarthria and ataxia in our 2 patients were their sudden paroxysmal occurrence and brief duration. The suddenness of onset of attacks of multiple sclerosis has long been recognized. Only recently has attention been paid to the study of new symptoms which occur and disappear within seconds or minutes. These phenomena are described by Brickner[13] as "transient, sudden, miniature attacks of multiple sclerosis," and the author suggests that vasospasm and consequent impairment of function are the mechanisms underlying the sudden onset and abrupt remission. Scotomas, blurring of vision, numbness, and paresthesias were among the symptoms noted. Sudden application of bright light, violent exercise, excitement, emotional stress, eating, and smoking were thought to be probable precipitating factors. Thygesen,[11] introducing the term "ictal phenomena," defined it as paroxysmal manifestations which, by reason of their almost momentary regression, usually escape objective evaluation, as distinct from seizures or attacks. In his series, paroxysmal accentuation of paresis and of visual symptoms was noted. While Thygesen suggested some of these might be of a neurotic nature, he considered vasospasm to be responsible in most cases and suggested the term "sublesional" attacks for their description. Other manifestations of the disease which sometimes occur in short attacks are trigeminal neuralgia[14] and vertigo. However, the transient nature of these symptoms is by no means the rule, and longer duration is frequently encountered. McAlpine and others[15] have reported a patient who presented with paroxysmal attacks of subjective lateral pulsion and paresthesias in the ipsilateral lower limb. These symptoms were attributed to lesions occurring in the vestibular system and brain stem.

CASE REPORTS

Case 1. A 27-year-old insurance salesman, J. E., had a three-week episode of numbness in the right arm and leg in April 1956. In July, he had a three-day episode of vertical nystagmus which he described as "jumping of eyes."

One evening in early August the patient suddenly found he could not speak clearly; he became dizzy for approximately one minute. The next day, he had frequent, similar paroxysmal attacks which began with dizziness followed by inability to articulate understandably, incoordination of the hands without weakness, and a tendency to stagger to the left when walking. In such an attack, he would try to continue speaking, but his words were poorly articulated and distorted beyond recognition. At times, in an effort to get a word out, the same syllable would be repeated—slightly resembling stuttering, but absence of rhythmic phonation and longer duration distinguished these episodes from stuttering. Because of this difficulty, the patient would stop talking, although he knew clearly what he wished to say and understood speech perfectly. If walking, he would tend to stagger and, therefore, usually stood still. After ten to fifteen seconds, the episode ceased as abruptly as it began. The attacks occurred regularly every three to five minutes and were slightly aggravated in frequency and severity when he was under tension.

The patient continued to work, although his attacks embarrassed him; for instance, when he spoke on the telephone, his speech would suddenly become unintelligible and he would have to later excuse himself. He found the sudden, transient ataxia while walking equally disturbing. To avoid embarrassment, he would retire to his office, avoid talking as much as possible, and communicate in writing. However, even with these handicaps, he was able to continue his work.

He was admitted to the Montreal Neurological Institute in August 1956. Examination showed paroxysmal attacks consisting of the following: dysarthria, incoordination, falling to the left, impaired rapid alternating movements, and writing difficulty which lasted ten to twenty-five seconds and occurred every three to six minutes. He had about 200 such attacks of similar pattern and duration every day.

Investigations in hospital included: hemoglobin and hematocrit determinations, and red and white blood counts, which were within normal limits. Fasting blood sugar was 88 mg. per cent; following a standard meal, blood sugar was 92 mg. per cent. Serology was negative in blood and cerebrospinal fluid. Lumbar puncture revealed crystal clear fluid under normal pressure; 86 lymphocytes per cubic millimeter; negative Pandy test; protein, 33 mg. per cent; sugar, 59 mg. per cent; chlorides, 690 mg. per cent. The colloidal gold curve was 5553321000. Electrophoresis of cerebrospinal fluid proteins showed a greatly increased gamma globulin level of 30% of cerebrospinal fluid protein—as compared to normal gamma globulin level of 5 to 10% of cerebrospinal fluid protein.

An electroencephalogram on August 22 was considered essentially within normal limits. A second electroencephalogram, September 11, was reported by Dr. Herbert Jasper as follows: "This electroencephalogram, taken during the patient's clinical attacks, indicates that the cortex itself does not seem to be involved in any way in these seizures. There is no evidence for an epileptiform disturbance, and there was little disturbance seen in normal background activity during attacks."

Radiologic investigations, which included roentgenograms of the skull and a pneumoencephalogram, were reported by Dr. D. L. McRae. The investigations showed some asymmetry of the skull—the floor of the skull being somewhat higher on the left. There was very slight atrophy of right frontal and parietal areas. No evidence was seen of an expanding intracranial lesion. A roentgenogram of the chest was normal. Dr. H. E. McHugh, consultant in otolaryngology, reported that the patient's audiogram was within normal limits. The vestibular tests showed the right side to be normal and the left slightly hypoactive.

While in hospital, the patient received a 10-mg. Dexedrine Spansule daily; Gravol suppositories; 25 mg. of Pacatal 3 times a day; 500 mg. of vitamin B_{12} intramuscularly once a day; 1 cc. of Beminal intramuscularly once a day; and a short therapeutic trial of 100 mg. of Dilantin twice a day. None of these medications seemed to produce any noticeable change in the attacks.

The patient was seen again on September 28, 1956. His attacks had diminished in frequency and occurred every ten minutes. He complained of some numbness in the left foot and lower leg, but there were no objective findings apart from his attacks.

On October 16, the attacks were following the same pattern. The patient had weakness of dorsiflexion and subjective numbness of the right foot. Numbness of the left lower leg had cleared. On November 14, a sudden improvement occurred. The number of paroxysms diminished to 2 or 3 a day and were less severe. The attacks finally stopped on December 20, 1956. The following month, the patient had a period of numbness involving the right side of his body. Onset was gradual and reached a peak in three days; then the symptom gradually subsided without objective findings. A month later, the patient had a number of attacks of right-sided numbness associated with some dysarthria. All these symptoms cleared within a week, and he has been symptom-free for the past eighteen months.

Case 2. A 33-year-old woodcutter, R. A., was first admitted to the Montreal Neurological Institute in November 1948. He had suffered partial loss of sensation of the right side of his body fifteen months previously. This loss was associated with staggering gait and attacks of blurred vision. The symptoms began to improve after twelve months and, on admission, he had only paresthesias in his finger tips, on contact, bilaterally. Speech was normal. The patient had pallor of the temporal half of the right optic disk, a left sixth nerve paresis and nystagmus on lateral and upward gaze. He showed deviation of the uvula to the right. His gait was wide based and slightly ataxic, and he had a tendency to fall to the left when he closed his eyes. The patient also had an intention tremor of the left side and an equivocal left plantar response with incoordination of the left leg.

Serology in blood and spinal fluid was negative. Cerebrospinal fluid protein was 26 mg. per cent and 33 mg. per cent on two different occasions. The Lange colloidal gold curve was 5432100000. Radiologic studies, including pneumoencephalography, revealed no evidence of a space-occupying lesion in the posterior fossa. There was slight cerebral atrophy. Multiple sclerosis was diagnosed.

In February 1949, the patient began to have attacks during which he could not articulate and had to stop talking. If he did not stop, his speech became quite unintelligible. The patient also had to stop walking during the attacks, because of a gait "like a drunkard." Onset and cessation of the attacks were sudden. The patient tried to avoid speaking and would stop walking because the momentary impairment caused him embarrassment. No impairment of consciousness or of muscular tone occurred. The frequency of attacks varied from ten to twenty a day; duration was approximately thirty seconds. When he was tired, frequency increased to 10 to 20 per hour. After a few months, the nature of the attacks changed. The patient had no ataxia, but attacks of dysarthria were superimposed on a slight, persistent articulation defect. Episodes of blurred vision were noted but had no relation to his paroxysms of dysarthria.

He was readmitted to the hospital in July 1950 with lateral and vertical nystagmus. The deep tendon reflexes were increased on the left side, associated with Hoffman's and Babinski's sign. The patient had a strongly positive Romberg test, marked dysarthria and ataxia, as well as impairment of fine movements and rapid alternating movements in both hands. An electroencephalogram done on this occasion revealed some minor irregularities which were consistent with a diffuse disorder of cerebral function. He was given

a brief therapeutic trial of 100 mg. of Dilantin three times a day while in hospital, but his attacks were not significantly altered. The attacks gradually subsided over a period of months.

In 1954, he was seen again, and, at that time, had severe gross nystagmus of the abducting eye on looking to right and to left and blurred vision, as well. The patient did not have dysarthria, but slowness of alternating movements of the tongue and limbs, absent abdominal reflexes, increased deep tendon reflexes on the left side, and an equivocal left plantar extensor response were noted. His gait was ataxic.

He was reexamined in January 1958, and his speech showed slight, persistent dysarthria without paroxysmal attacks of dysarthria or ataxia. Neurologic signs showed no essential change during the past three years, except for a definite left plantar extensor reflex. Diagnosis of multiple sclerosis appeared to be confirmed.

DIFFERENTIAL DIAGNOSIS

The nature of the paroxysmal attacks presented by these patients offered a problem in diagnosis. The following possibilities were considered:

Focal cerebral seizures. While the occurrence of focal cerebral seizures in multiple sclerosis is not as rare as was once thought, the following points seem to exclude them in these patients:

1] No impairment of consciousness or memory
2] No tonic or clonic movements
3] No recordable alterations in the electroencephalographic tracing during an attack
4] Signs suggestive of cerebellar dysfunction

Attacks of vestibular dysfunction. Although a vestibular origin was considered in the first patient—who described dizziness as a part of his attacks—he had no alteration in the attacks with postural changes. Nausea and vomiting or nystagmus were not associated. Movement did not bring about or accentuate the attacks. No lateral pulsion or swaying was seen. The disturbance of speech was the most dramatic symptom, and the one which caused the patients the most concern.

Hysteria. The following points make this unlikely: objective signs of definite neurologic lesions; abnormal colloidal gold curve and an elevated gamma globulin; absence of any previous personality maladjustment or psychiatric disturbance.

Space occupying lesion. This possibility was ruled out in both cases.

Stuttering. The patients had no previous history of speech disturbance, and no stuttering ever had been present in either. The periodicity and time course of the paroxysmal attacks of dysarthria were quite unlike those of stuttering.

Finally, the diagnosis of multiple sclerosis was thought to be well established on the basis of the history, examinations, and subsequent course of the illness.

DISCUSSION

If the symptomatology of the attacks had been referable to a cortical localization, the hypothesis of their epileptic nature would have proved very attractive. Interference with speech and consequent aphasic arrest have been described by Penfield and Jasper[16] as occurring in discharge of the dominant hemisphere involving cortical speech areas. Epileptic discharge in a portion of the motor area devoted to the mouth, respiration, or vocalization interferes with speech by creating a motor block. These types of paroxysmal dysphasia have recently been studied by Hecaen and Piercy.[17] However, the paroxysmal attacks described in these patients showed no clinical resemblance to attacks of aphasic arrest. Furthermore, no cortical discharge was recorded in the electroencephalogram during an attack.

The association of paroxysmal dysarthria, ataxia, and incoordination seems to point to an origin in the cerebellum or its connections in the brain stem.

Subcortical (extracentrencephalic) seizures as defined by Penfield[16] arise from discharge in the brain stem or spinal cord and are characterized by motor manifestations, such as tonic spasms or clonic jerks of muscle fasciculi or muscle groups.[16] Since the attacks presented by our patients had no motor components, it is unlikely that they were subcortical seizures.

What then in the pathology of multiple sclerosis is the mechanism responsible for the appearance of paroxysmal dysarthria and incoordination? Could vasospasm (Brickner[18]) account for a symptom which appeared with such regularity and frequency? We think not. Neither do the findings, symptoms, or course of illness suggest insufficiency of the vertebral-basilar arterial system.

Lumsden[15] considers that "partially or wholly denuded axons are more vulnerable than normal axons to a variety of both exogenous and endogenous agencies." That such a factor is present in the symptoms here discussed is very likely. Indeed, it would be difficult to postulate morphologic changes which would cause an attack and then reverse in such a short time. Apparently, the paroxysmal nature of the symptoms indicates a disorder of function rather than a morphologic change. The underlying neurophysiologic mechanism might be a conduction disorder determined by a rapidly reversible disturbance of metabolism of the myelin sheath or its supporting oligodendroglia.

The course of this symptom of paroxysmal dysarthria is remarkable because, unlike other speech disturbances in multiple sclerosis, prognosis seems good, and both patients discussed here have had complete remissions of this symptom.

CONCLUSIONS

1] Paroxysmal dysarthria and ataxia in 2 patients with multiple sclerosis are reported. These occurred in brief attacks lasting ten to twenty seconds, with sudden onset and cessation, and recurred over a period of months, eventually disappearing completely.

2] The various forms of disturbance of speech described in multiple sclerosis are reviewed. A search of the literature has failed to reveal any similar cases of paroxysmal dysarthria.

3] The differential diagnosis is discussed and, for the reasons presented, it is suggested that the attacks may originate in a disturbance situated in the cerebellum or in its connections in the brain stem.

4] The implication of these attacks in the pathogenesis of multiple sclerosis is briefly discussed.

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REFERENCES

1. Charcot, J. M.: Lecons sur les maladies du système nerveux. Receuillies et publiées par D. M. Bourneville. Bureaux du Progres Médical Paris 1:221, 1892.
2. Ellermann, M.: Kliniske Studier over dissemineret Sklerose of beslaegtede Lidelser. Diss. Copenhagen, 1937.
3. Brown, M. R., and Putnam, T. J.: Remissions in multiple sclerosis. Arch. Neurol. & Psychiat. 41:913, 1939.
4. Oppenheim, H.: Lehrbuch der Nervenkrankheiten. 6th ed., Berlin, 1913, Verlag S. Karger, pp. 435-437.
5. Lahr, quoted by H. Oppenheim: op. cit. p. 437.
6. Lori, quoted by H. Oppenheim: op. cit. p. 437.
7. Leube, W.: Ueber multiple inselförmige Sklerose des Gehirns und Rückenmarks. Deutsches Arch. klin. Med. 8:1, 1871.
8. Rethy: Die laryngealen Erscheinungen bei multipler Sklerose, Vienna, 1907.
9. Scripture, E. W.: Records of speech in multiple sclerosis. Brain 39:455, 1916.
10. Muller, Ragnar: Studies on disseminated sclerosis. Stockholm, 1949, p. 24, p. 91.
11. Thygesen, Paul: The course of disseminated sclerosis. Copenhagen, 1953, Rosenkilde and Bagger, p. 23, p. 124.
12. Lesny, I., and Polacek, L.: Anticoagulant therapy in disseminated sclerosis. Casop. lék. cesk. 88:113, 1949.
13. Brickner, R. M.: The significance of localized vasoconstriction in multiple sclerosis. Ass. for Res. in nerv. and ment. dis. 28:236.
14. Meredith, J. M., and Horrax, G.: Occurrence of trigeminal neuralgia in patients having multiple sclerosis. J. Nerv. & Ment. Dis. 82:497, 1935.
15. McAlpine, D., Compston, N. D., and Lumsden, C. E.: Multiple sclerosis. London, 1955, E. & S. Livingstone.
16. Penfield, W., and Jasper, H. H.: Epilepsy and the functional anatomy of the human brain. Boston, Little, Brown and Co., p. 366, p. 377.
17. Hecaen, H., and Piercy, M.: Paroxysmal dysphasia and the problem of cerebral dominance. J. Neurol. Neurosurg. & Psychiat. 19:194, 1956.

Use of Echoencephalography

M. de Vlieger, M.D., and H. J. Ridder, A.M.I.E.E.

ULTRASONIC inspection is making progress in the medical field as well as in industry.

At first, ultrasonics did not give the expected result in the diagnosis of intracranial processes. This was principally because the transmission method with continuous sound was used. By this method, only the differences between the transmitted and the received energy are measured; the scattering of sound in the bone, the thickness variations of the skull, and difficulties with the coupling between probes and head directly influence the results.

Dussik,[1,2,3] Ballantine,[4,5] and Hueter[6] and associates have tried to get a picture of the ventricles by this transmission method—the so-called hyperphonography. However, the ventricle picture was not as clear as a pneumoencephalogram. Leksell,[7] however used the reflection or echo method and found a midline reflection which was displaced in patients with extradural hematoma. According to Leksell, the cause of this midline reflection is unknown.

BASIC ULTRASONICS

In industrial testing technics, a beam of high frequency vibrations is passed into the material being tested and reflections are obtained from the surfaces and from various physical discontinuities within the piece. Generally, frequencies from 1 to 6 mc. per second are used, extended in special cases from 0.25 to 10 or even 25 mc. per second. Short pulses of high-frequency electrical energy are applied by a transmitter to a piezoelectric crystal, which produces the mechanical vibrations for transmission into the material being tested. The reflections of these pulses can be picked up and interpreted.

The reflected pulses are picked up by the same or a second similar crystal, converted into electrical signals, amplified, and fed into a cathode-ray oscilloscope. In the usual type of equipment, the trace is vertically deflected by these signals.

As the horizontal deflection of the trace is a linear function of time, the various reflections are displayed in time sequence, and their distances from the transmitter crystal can be deduced. This type of presentation is called the A-scan.

In industrial testing, 3 types of vibrations are applied—longitudinal or compression waves, transverse or shear waves, and surface waves. For the examination of intracranial processes, however, only longitudinal waves can be employed.

Ultrasonic testing reveals physical differences inside the object under test but does not give information about the exact nature of these differences. The effective variations are in acoustic impedance, a function of density and elastic properties which determines the quantity of energy passed from one element of structure to the next and, consequently, the proportion reflected. Of course, the actual amount of reflected energy is determined by the size and shape of the reflecting surface.

METHOD

The measurements were carried out with normal industrial ultrasonic equipment of Drs. J. and H. Krautkrämer, type USIP 9. The probes used were provided with barium titanate mosaic crystals, which could be used together or as separate transmitter and receiver. Generally, 1-mc. probes were used, but 2 mc. was also applied.

At first, glycerin was used as coupling fluid. A better medium proved to be a mixture of syrupus glucosi with syrupus simplex, as this corresponds better acoustically with hair and skull. The main advantages are that the coupling is more stable and the head need not be shaved.

Dr. de Vlieger is from the Neurological Department of the Municipal Hospital, Coolsingel, in Rotterdam, The Netherlands.

Mr. Ridder is from the Ultrasonic Laboratory of the Röntgen Technische Dienst N.V., Rotterdam, The Netherlands.

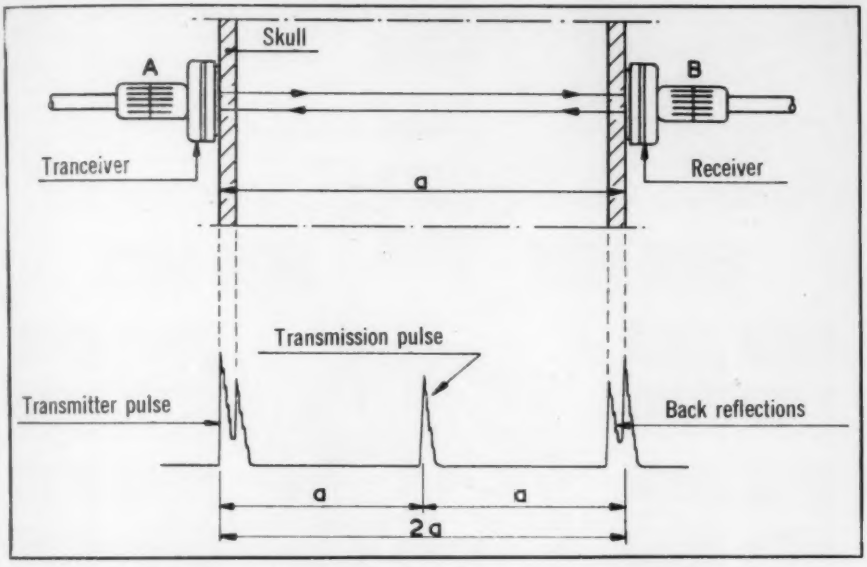


Fig. 1. Schematic presentation of screen image with center indication

RESULTS

Midline. When ultrasound is transmitted to the lateral surface of the skull in a direction perpendicular to this surface, a reflection of high amplitude nearly always is received from the inner surface of the opposite side of the skull. Under normal conditions, a somewhat smaller reflection is seen at half the distance between the transmitting pulse and this back reflection. The smaller reflection is called the midline reflection because it must originate from some surface in the midline of the skull.

Ultrasonic examinations were carried out identical with those described by Leksell.[7] However, radiographs indicated displacement of the midline in 2 patients which was not noted during ultrasonic examination. This was apparently due to the fact that the screen image was too small and very small displacements of the midline reflection showed relatively large. After the screen image had been enlarged from 2 to 4 in., such errors no longer occurred.

The determination of the exact center on the time base was also improved by using two probes or scanners — 1 tranceiver (transmitter and receiver combined) and 1 receiver. The probes are placed on either side of the head exactly opposite each other. Sound pulses from the transceiver pass through the brain, are reflected from the opposite side of the skull, and reach the tranceiver again — thus passing through the brain twice. This is calibrated on the screen as 1 x the distance.

Not all energy is reflected from the opposite side of the skull; part passes through the skull and is picked up by the receiver. This gives rise to a transmission pulse which will appear at exactly half the distance (Fig. 1).

After these improvements, cause of the midline reflection was sought. During an autopsy, 4 measurements were made, and the screen images were photographed (Fig. 2): on the skull with skin; on the skull without skin; directly on the brain with falx cerebri; and on the brain immersed in water without falx cerebri.

During these measurements, it became evident that the midline reflection was not caused by the falx cerebri but by the longitudinal fissure. On several occasions, a double midline

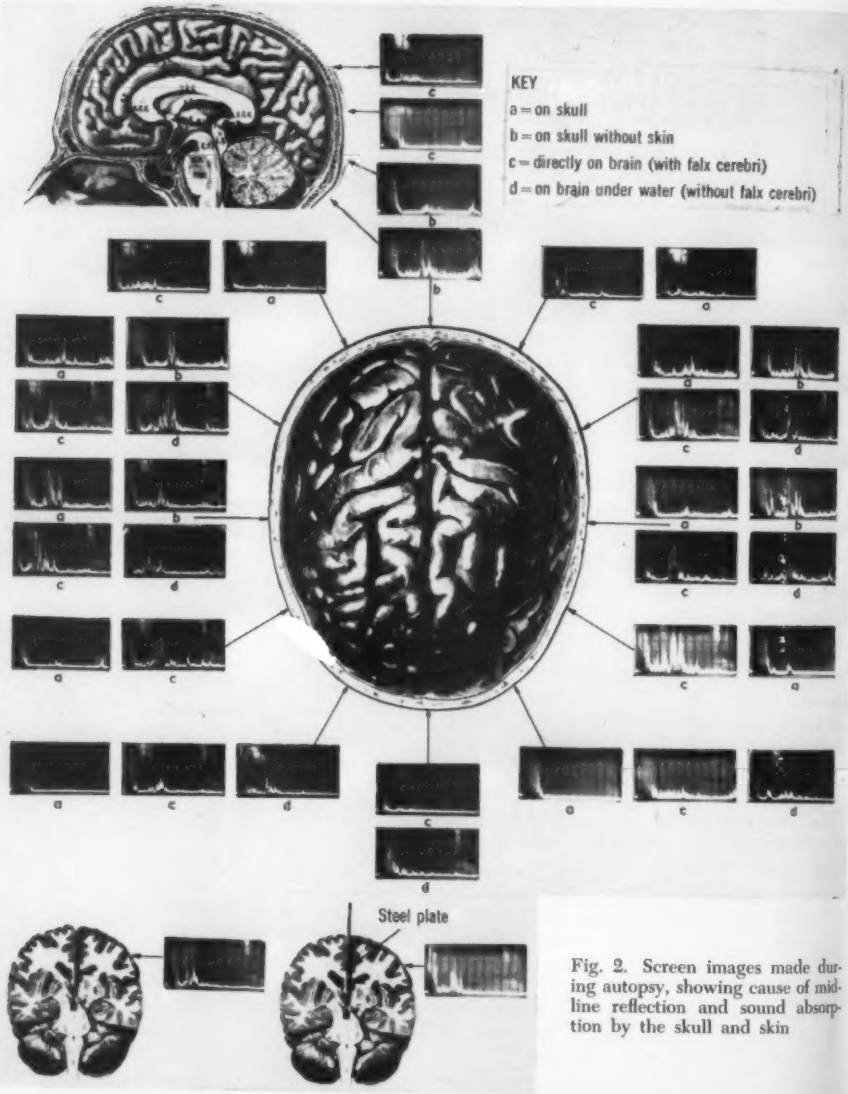

KEY
a = on skull
b = on skull without skin
c = directly on brain (with falx cerebri)
d = on brain under water (without falx cerebri)
Steel plate

Fig. 2. Screen images made during autopsy, showing cause of midline reflection and sound absorption by the skull and skin

reflection was seen which hampered the interpretation of the screen image (Fig. 3).

This double reflection can be explained as follows: The ultrasound pulses are reflected at the boundary of brain tissue and cerebrospinal fluid. When the hemispheres are close together, the 2 reflections from the transition of brain tissue – cerebrospinal fluid – brain tissue will be visible as 1, because they overlap on the screen.

When the longitudinal fissure is wider, the reflections can be seen separately. This was

proved by placing a thin steel blade in the longitudinal fissure, the reflection of which appeared exactly between the double midline reflection.

Ventricular system. By transmitting systematically from ear to ear across the coronary line, it was possible to localize the ventricle system.

Under favorable conditions, the width of the third ventricle can be calculated from these reflections. In a patient examined in this way, a pneumencephalogram was used for comparison with the reflection images which were photographed.

An over-all view of these pictures is given in Figure 4. This view might be of special use in patients with hydrocephalus to determine the size or relative value of the ventricular system in order to establish, by periodic examinations, the course of any changes.

Echo pulsation. In accordance with Leksell's[7] findings, vertical pulsations of various reflections were observed (Fig. 5). These pulsations are synchronous with the heartbeat and could be registered by coupling the ultrasonic equipment by a gating system to the last amplifier stage of a Kaiser electroencephalograph. Sometimes the pulsations are approximately 180° out of phase with each other. When the jugular veins were compressed by the Queckenstedt method, the pulsations were suppressed. Probably, the pulsations are caused by periodically occurring changes in the shape of reflecting surfaces. This is supported by the following experiment (Fig. 6).

In a Perspex water tank, a plastic bag filled with water was placed approximately 10 cm.

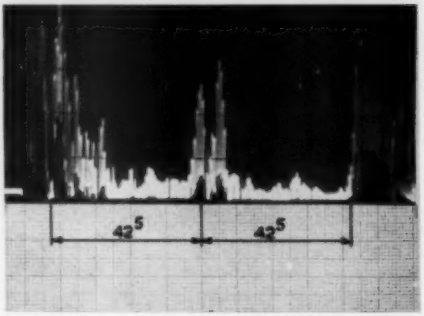


Fig. 3. Screen image with double midline reflection

in front of a tranceiver probe identical to that used for echoencephalography. The walls of the plastic bag were kept 3 mm. apart and, except for a small tube, the bag was sealed.

By blowing in this tube, variations in pressure could be obtained. At zero pressure, 2 reflections of the same height were received. By changing the pressure in the bag, the reflections varied in amplitude, synchronous with changes in pressure.

This can be explained as follows: The ultrasound pulses are first reflected on a convex surface and scattered. Only a small part of the energy will reach the tranceiver again, causing a small echo. The second reflection will take place on a concave surface, causing a converging beam. The greater part of the energy will now reach the tranceiver and will give rise to a large echo. When pressure is decreased, the process is reversed, and the pulsations are approximately 180° out of phase.

In case of cerebral reflection, we have the

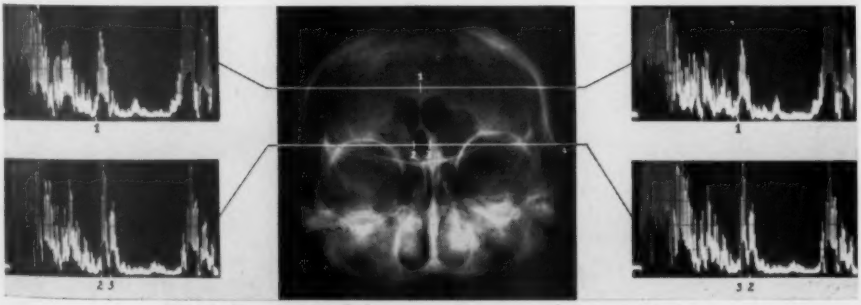


Fig. 4. Pneumoencephalogram with corresponding screen images

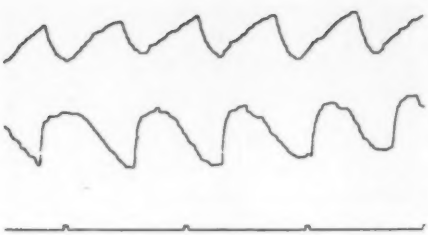


Fig. 5. Recording of double midline pulsations. Recording of each reflection was made separately.

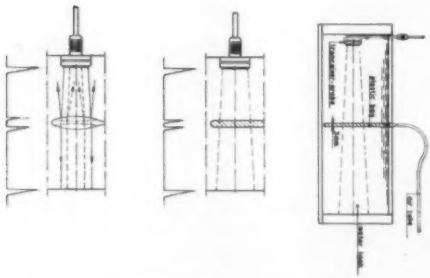


Fig. 6. Schematic view of experiment to probe nature of the pulsations

following situation: When the cerebral volume increases, the hemisphere approaches a more spherical shape. So the first midline surface on which reflection takes place is more concave; consequently, more energy is reflected toward the tranceiver, resulting in a greater echo on the screen. The reverse is the case with the second surface, which is convex to the sound beam; the second midline reflection will be smaller.

During the Queckenstedt test, when the cerebral volume is increased the amplitude of the first echo increases too, while the second diminishes.

During cardiac systole, arterial blood is injected into the brain so that the brain volume increases. Therefore, it is to be expected that during the systole the first echo increases and the second one decreases. This deduction is confirmed by the observation of the midline-echo pulsations on the screen. Pulsations in a horizontal direction were not visible because of small pressure variations involved.

Clinical application. The midline reflection was determined in 47 patients (see table). In 21 patients with tumors or intracerebral and extracerebral hematomas, a displacement of this midline reflection could be established which corresponded to the displacement caused by the tumor or hematoma. Frontal tumors often do not cause displacement of the midline when transmitting temporally.

Among the patients without displacement of the midline reflection were several with cerebral tumors. Apparently, however, an angiogram, pneumoencephalography, or radiograph did not show a displacement either. Patient No. 37 is an instance where a displacement was observed more frontally, but not temporally.

CASE HISTORY

In 1957, Patient J. became apathic and demented. He complained of headaches. Neurologic examination, electroencephalography, and angiogram indicated a left frontal tumor. The radiograph showed a slight pineal shift to the right.

Echoencephalography. The echoencephalogram showed the following:

Temporal, no displacement of the midline reflection

Laterofrontal, displacement of approximately 1 cm. to the right. The screen image was locally disturbed by many small reflections (Fig. 7).

The operation report confirmed the diagnosis.

Pathology. Oligodendroglioma with calcification was found pathologically.

DISCUSSION

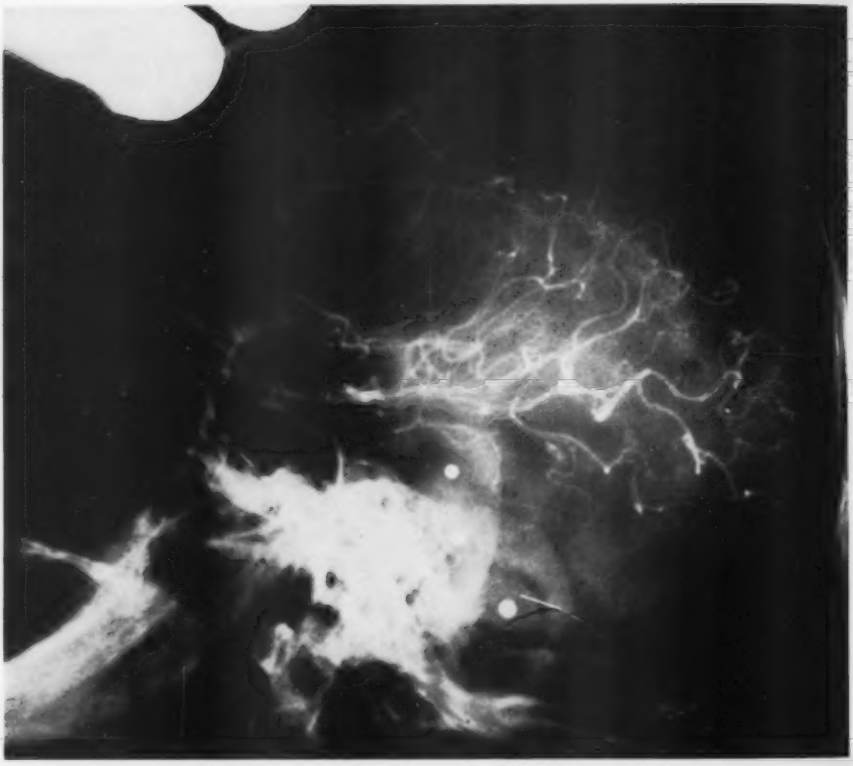
Ultrasonic measurements were carried out to determine the physical and anatomic bases for the various reflections obtained from the brain which, according to Leksell, were not yet clearly understood.

During these measurements, new facts were brought to light. It could be demonstrated that significant reflections could be obtained from the transition between brain tissue and cerebrospinal fluid. This seems contradictory to the statement of Güttner[8] and associates, who assert that the reflection-coefficient between brain tissue and cerebrospinal fluid is so small that the reflections will not rise above the noise level because of the scattering of the sound beam by various causes.

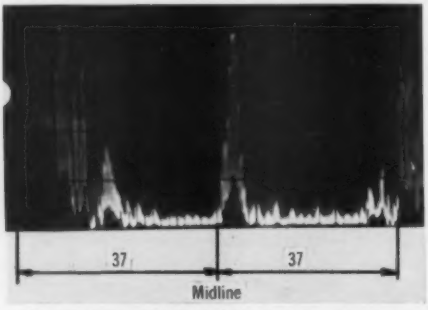
However, reflections were obtained — some with almost the same amplitude as the reflection from the opposite side of the skull. The

Patient No.	Displacement of midline	Diagnosis	Details
1	None	Subarachnoid hemorrhage	No displacement on angiogram
2	Right	Astrocytoma, left frontotemporal	Displacement to right on ventriculogram
3	None	Cerebral thrombosis	No displacement on angiogram
4	None	Epidural hematoma on left	Pineal body displaced to left
5	None	Hydrocephalus	No displacement on ventriculogram
6	None	Hydrocephalus	No displacement on ventriculogram
7	Right	Oligodendroglioma, left frontal	Displacement to right on angiogram
8	None	Subdural hematoma on right	Displacement to left on angiogram
9	Left	Astrocytoma, right frontobasal	Displacement to left on angiogram
10	None	Cerebral concussion	Radiography normal
11	None	Cerebral concussion	Radiography normal
12	None	Encephalitis	Radiography normal
13	None	Hydrocephalus	No displacement on ventriculogram
14	None	Cerebral concussion	Encephalogram normal
15	Right	Astrocytoma, left temporal	Displacement to right on angiogram
16	Left	Falx meningioma, right frontal	Displacement to left on angiogram
17	Left	Subdural hematoma on right	Displacement to left
18	Right	Meningioma, left frontoparietal	Displacement to right on angiogram
19	Right	Glioma, left frontal	Displacement to right on angiogram
20	None	Right central tumor	No displacement on angiogram
21	Right	Glioblastoma multiforme, right parietal	Displacement to right on angiogram
22	Left	Right temporal glioma	Displacement of ventricles to left on pneumencephalogram
23	None	Tetany	Radiography normal
24	None	Vascular accident	Middle cerebral artery closed
25	None	Meningitis	Radiography normal
26	None	Passing visual disturbances	Radiography normal
27	None	Carcinoma metastasis, posterior fossa	No displacement on ventriculogram
28	None	Cerebral concussion	Radiography normal
29	Left	Subdural hematoma on right	Displacement to left on angiogram
30	None	Neuritis of optic nerve	No displacement on pneumencephalogram
31	None	Concussion	Radiography normal
32	None	Glioma, right frontal	No displacement on angiogram
33	Left	Subdural hematoma on right	Displacement to left on angiogram
34	Left	Acute subdural hematoma	Operation confirmed displacement
35	None	Vascular accident in cerebro	Radiography normal
36	None	Pons tumor	No displacement on pneumencephalogram
37	Left	Oligodendroglioma, right frontal	Displacement to left on angiogram
38	None	Traumatic capitis	Dubious fracture line on radiogram
39	None	Atypical migraine	Encephalogram normal
40	Left	Glioma, right frontotemporal	Angiogram indicated displacement to left
41	Right	Bilateral subdural hematoma	Left-sided hematoma larger than right-sided one
42	None	Mesencephalic tumor (glioma)	No displacement on angiogram
43	Right	Astrocytoma on left	Displacement to right on angiogram
44	Right	Intracerebral hematoma, left frontoparietal	Slight displacement on angiogram
45	Left	Astrocytoma, right frontal	Displacement to left on angiogram
46	Left	Glioma, right parietotemporal	Displacement to left on angiogram
47	Left	Glioma in right wall of third ventricle	Displacement of the third ventricle to left on ventriculogram confirmed by operation

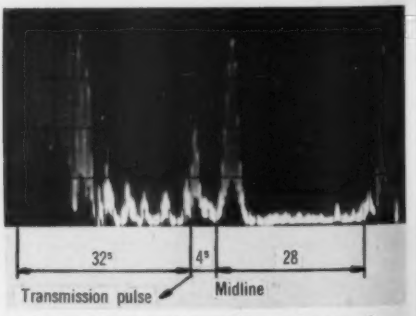
Figure 7



Angiogram of patient (No. 37) with left frontal tumor



Screen image with midline reflection in center (temporal)



Screen image with midline reflection displaced 9 mm. from transmission plate

quantity of reflected energy is determined by the acoustic impedance, a function not only of the density, but also of the elastic properties of the 2 substances. In this respect, measurements were carried out on the transition of gelatin with a sound velocity of 1.50×10^5 cm. per second and water with a sound velocity of 1.49×10^5 cm. per second at a temperature of 23° C.

The screen image was photographed to show the ratio in amplitude between the transition gelatin-water and water-air. A roentgenogram was made of the transition gelatin-water and the density of the 2 substances was measured with a Baldwin Densitometer. The values received were 0.80 for gelatin and 0.82 for water, a difference of 0.02 which cannot be determined visually on a roentgenogram. The screen image is shown in Figure 8.

The reflection method appears very promising for the examination of the brain, especially for the speed with which, in acute cases, important information can be obtained without ill effects for the patient.

Besides indicating the presence of intracerebral and extracerebral hematomas and tumors, the determination of the size of the ventricular system or its relative value is of importance for the study of hydrocephalus — especially since the examination is rather simple and can, if necessary, be done daily without any ill effects.

Another advantage of the reflection method is the possibility of registering pulsations from which a relative value for the change of the cerebral volume might be deducted.

Although the hyperphonography of Dussik and associates does not give a clear picture of the ventricles because of physical causes, a possibility exists, although not yet pursued by us, of using the reflection method with B-scan presentation. According to this method, a section of the part examined is made visible on a cathode-ray tube. This can be done by moving the horizontal deflection of the trace vertically across the screen synchronous with the movement of the tranceiver probes. The reflections obtained will suppress the brilliance of the trace, and, when a cathode-ray tube with long afterglow is employed, a complete image is built up similar to that of a television picture.

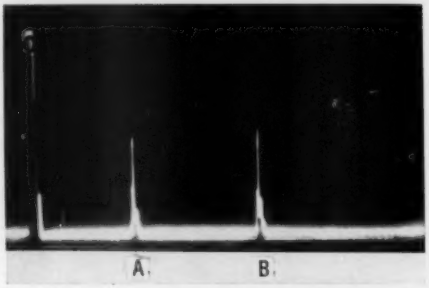


Fig. 8. Screen image showing reflection of the transition (A) gelatin-water and (B) water-air

This method is already used in industry and has also been used in cancer research. The examination of the brain has not been carried out in this way as far as we know.

SUMMARY

This paper deals with the ultrasonic inspection of the brain by the reflection method in order to establish the cause of displacements of the midline. Of 47 patients examined, 21 had displacement of the midline caused by a cerebral tumor or an intracerebral or an extracerebral hematoma. In the 2 patients, a displacement could not be established because the equipment had not been fully adapted for the purpose. After some alteration, no more trouble occurred.

REFERENCES

1. Dussik, K. T., Dussik, F., and Wyt, L.: Auf dem Wege zur Hyperphonographie des Gehirnes. Wien. med. Wchnschr. 97:425, 1947.
2. Dussik, K. T.: Zum heutigen Stand der medizinischen Ultraschallforschung. Wien. klin. Wchnschr. 61:246, 1949.
3. Dussik, K. T.: Weitere Ergebnisse der Ultraschalluntersuchung bei Gehirnerkrankungen. Acta neurochir. 2:379, 1952.
4. Ballantine, H. T., Jr., Bolt, R. H., Hueter, T. F., and Ludwig, G. D.: On the detection of intracranial pathology by ultrasound. Science 112:525, 1950.
5. Ballantine, H. T., Jr., Bolt, R. H., and Hueter, T. F.: On the use of ultrasound for tumor detection. J. Acoust. Soc. Am. 26:581, 1954.
6. Hueter, T. F., and Bolt, R. H.: Ultrasonic method for outlining the cerebral ventricles. J. Acoust. Soc. Am. 23:160, 1951.
7. Leksell, L.: Echo-encephalography; detection of intracranial complications following head injury. Acta Chir. scandinav. 110:301, 1955.
8. Güttner, W., Fiedler, G., and Patzold, J.: Ueber Ultraschallabbildungen am menschlichen Schädel. Acustica 2:148, 1952.

Drugs for treatment of depression

John C. Saunders, M.D., and Nathan S. Kline, M.D.

A REVIEW of historic therapies for depressive syndromes indicates that the administration alone of a central nervous system stimulant is not enough.

We know that most central nervous system stimulants are not highly selective in their sites or modes of action, even though we classify them as stimulants of the spinal cord, brain stem, and cerebral cortex. In order to alleviate the depressive signs and symptoms, a preparation must increase the driving forces basic to human nature. These complex forces are related to psychobiologic factors.

The concept of psychic energy goes as far back as Aristotle who called it *horme*, meaning "drive" or "urge." Freud gave such an energy concept the name, libido, and associated it with the transformation of energy inherent in the sex instinct. Jung uses the word "libido" to encompass the concept of psychic energy from any source.

Significantly, the psychopharmaceutical agent iproniazid (Marsilid) is highly effective in the treatment of various depressive manifestations. Marsilid increases psychic energy but occasionally reduces sexual energy. Therefore, the type of psychopharmaceutical preparation for depressive states is one that increases the biologic energy necessary for psychobiologic drive.

The classification of mental diseases is still confused, possibly because defining psychic entities is difficult. Many scientific workers are able to investigate and report in an area where scientific exactness is obtainable, but to report one's observations in psychiatric phenomena leaves much to be desired. This is particularly true in depressive states, since this manifestation may be seen in phases of all psychiatric disorders.

In the original report from Rockland State Hospital on Marsilid,[1] we stated that our hypoactive patients were withdrawn, regressed, deteriorated, colorless, and of flattened affect; although this limited group was schizophrenic, other studies have included all the known diagnostic classifications if depressive or withdrawal phenomena are present. Since that report, we have treated all forms of depression and withdrawal—even suicidal and autistic—with a high degree of response.

ANTIDEPRESSIVE THERAPY

The production of anaphylactic shock by transfusing calf's blood to relieve manic-depressive conditions was reported by Denis from France before 1682. In 1756, Richard Lovett used electricity successfully in the treatment of mental disease, and, in 1785, William Oliver used camphor in the treatment of manic-depressive psychoses.

In 1927, Sakel introduced insulin-shock treatment for the whole spectrum of psychoneurotic disorders. Later, Meduna used camphor, and then, Metrazol, as convulsive agents in treating schizophrenic patients. The results with Metrazol and other convulsants in treatment of depression are controversial.

The next step in the use of convulsive therapy came from Cerletti and Bini when they applied electroshock. Choices for the production of convulsions, are considerable, since approximately 4,000 papers have been published on the various aspects of this form of therapy in mental disease.

The metabolic changes from these forms of convulsive therapy have several factors in common. Originally it was assumed that insulin acts by producing a drop in blood sugar. Metrazol also produces a lesser drop, and both have in common a decrease in fat content and alkaline shift, followed by a rapid reversal of these substances due probably to increased activity of the adrenal gland indicated by a rise in urinary 17-ketosteroids. What we see is

From the Research Facility, Rockland State Hospital, Orangeburg, N. Y., and College of Physicians and Surgeons, Columbia University, New York City.
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a picture of metabolic changes that affect the central nervous system and are associated with convulsions. Electroshock therapy reportedly produces comparable metabolic changes. The use of these forms of therapy is restricted because of difficulties of administration, poor patient acceptance, and relatively low degree of clinical improvement.

Both traditional and recent psychopharmaceutical agents have been tested, and response depends on the diagnosis and severity of the neuropsychiatric condition. However, as a rule, therapeutic effect has not equalled pharmacologic action. This may be due to diffuse activity which occurs in the central nervous system and on end organs. Caffeine is a good example, since it stimulates all areas of the cerebral cortex and the brain stem as well. In therapeutic doses, caffeine improves both sensory and motor function but, in large doses, the entire central nervous system may be stimulated indiscriminately and depression follows. Apparently, caffeine is useful only in slight neurotic depression.

The use of the many sympathomimetic amines has been widespread. The synthesis of these compounds comes from the pharmacologic action of ephedrine and epinephrine. Ephedrine is a stable and orally active central stimulant, whose use as a stimulant has been largely restricted to narcolepsy and cataplexy and as an analeptic in overdosage for central depressants. Ephedrine also inhibits amine oxidase and is not metabolized by either amine or phenol oxidase.[2]

Another potent inhibitor of amine oxidase is amphetamine. The amphetamines are potent nervous system stimulants and this, along with their psychic effects, makes them useful in psychogenic disorders with primary depressive manifestations. The clinical value of the amphetamines is limited to small doses in mood disorders, since large doses are frequently followed by depression, generalized irritability, and motor hyperresponsivity. Psychotic, depressed patients respond poorly, if at all; therefore, the application of amphetamines in psychiatry is restricted.

Except for methylphenidate (Ritalin),[3] our experience with other sympathomimetic agents has been equally disappointing. However, therapeutic value of Ritalin is limited largely to the neurotic depressive states or as a counteractant to tranquilizer-induced lethargy and depression.

Rauwolfia alkaloids have been used as tranquilizers by the natives of India for many centuries; cocaine, an Erythroxylon alkaloid, has long been employed as a central nervous stimulant in Peru and Bolivia. At one time, cocaine was used as a cortical stimulant but is seldom employed now because of extreme toxicity. Cocaine inhibits amine oxidase,[4] an enzyme system that oxidizes epinephrine. Pharmacologically, cocaine potentiates the response of the sympathetic nervous system to epinephrine and norepinephrine; also, cocaine may increase the permeability of adrenergic nerve cells to activating agents. This combined action directs us to the next compound, Marsilid, which has been effective in the treatment of all phases of depression.

METHOD

The central nervous system stimulants reviewed are all capable of inhibiting amine oxidase. Marsilid is a potent inhibitor of amine oxidase with a high specificity for the brain. Our report is based on twenty months' observation of approximately 450 patients. Procedure for treatment and theoretic possibilities about Marsilid's mode of action and efficacy in treatment of depressed and regressed psychoses were presented in previous reports.[1,5]

Marsilid was used in all types of depressive and withdrawal states — reactive depression, manic-depressive psychoses, involutional psychoses, regressed and withdrawn schizophrenia, childhood schizophrenia of the infantile autistic type, and in patients with suicidal tendencies. If the patients were depressed or withdrawn, they were selected regardless of diagnostic category. However, those treated with Marsilid were acute and chronic, neurotic and psychotic, hospitalized and nonhospitalized.

The desired therapeutic response is obtained without psychologic toxicity. The only serious instance of somatic toxicity was a 13-year-old schizophrenic (infantile autistic type) who died of jaundice after thirty-six days of therapy. No autopsy was performed because of religious reasons. Laboratory findings were all normal when medication was started; however, in

1954, jaundice had been observed with associated laboratory findings. Therefore, history of liver disease may be a contraindication for Marsilid therapy. However, this liver syndrome resembles viral hepatitis. In the children's unit, 5 patients have had jaundice since the patient reported was observed, but none received a phrenotropic agent. Possibly, the death was a result of infectious hepatitis, and Marsilid may have augmented the process. The mortality rate of postmenopausal patients and children to infectious hepatitis is high.

The childhood schizophrenia patients of the infantile autistic type were treated with 10 mg. of Marsilid three times a day.[6] Purpose of therapy was to see if Marsilid would alleviate muteness, lack of interpersonal relationships, and withdrawal tendencies. During the second month of Marsilid therapy, 35% of the children became more aware of their surroundings, personal relationship improved, vitality increased, tenseness lessened, and more attempts were made to use speech.

About 35% of the children were easier to manage in cottage life than they were when receiving the tranquilizers. Part of the remaining group became extremely irritable and overactive, and others developed insomnia; but these are indications for dosage adjustment. Previous studies with classic psychomotor stimulants have frequently produced irritable, overactive, sleepless reactions.

Many reactive depressions in which the patients feel inadequate, unhappy, or uninterested have responded within a few days after Marsilid was administered, although other depressions may require several weeks of therapy. Both neurotic and psychotic depressive reactions are relieved as the neurotic's ability to concentrate improves and the psychotic's memory impairment or feelings of unreality disappear. Significantly, this response contrasts with that produced by tranquilizers; the depressive patients apparently are completely relieved of their psychopathology after Marsilid has been administered, while the tranquilizers appear to largely relieve symptomatic response — except for the 10 to 15% of patients who are able to leave the hospital.

Manic-depressive reactions have responded to Marsilid therapy. This group of affective reactions has created classification problems, and Dr. William A. White wrote, "The whole question of the differentiation of some cases of manic-depressive psychosis from dementia praecox involves the greatest nicety of observation, interpretation and judgement." The exceptionally promising results obtained with Marsilid in this group of patients may indicate that an etiologic[7] basis has been found for those free of environmental or psychogenic factors. Since many of these patients have suicidal tendencies as the depression recedes, the need for proper care during convalescence increases; the patient's energy level at this time is sufficient to carry out his intentions. Marsilid, because of its relatively rapid action, has been able to protect patients in this stage.

TREATMENT FOR PATIENTS WITH SUICIDAL TENDENCIES

The one remaining indication for electroconvulsive therapy is the *actively* suicidal patient who is not under supervision.

Suicide is a major cause of death among psychiatric patients. The suicidal tendency is common to all forms of mental disease and is even found in many so-called healthy persons. The psychiatric concepts given to explain this act are many. However, these concepts may be inadequate, since they are almost entirely psychodynamic and do not seriously include cases based on organic etiology. Lewis[8] presented the equation "suicide equals depression" and many investigators in this field believe that extreme depression will cause the patient to destroy himself. Our impression is that this is not entirely true, since impulsiveness or feelings of omnipotence may also be involved.

Marsilid[9] has been given intramuscularly to patients threatening suicide either by speech and/or behavior. Results and improvement were rapid.

A depressed young man had the habit of suspending himself with a piece of clothing around his neck until he became cyanotic. He was given Marsilid intramuscularly, and his depression subsided. Medication was discontinued, and, a few days later, he was found hanging from a window guard. Repeated and prolonged Marsilid therapy has ended this patient's depression, and he no longer has suicidal thoughts.

Patients[10] so depressed that they attempted to starve themselves and were fed by tube received 25 or 50 mg. of Marsilid intramuscularly twice daily and were eating in one and a half to two hours after initial injection.

The involutional, psychotic depressive reaction, one of the most frequent in psychiatry, has usually been treated with electroconvulsive therapy. Again we have found Marsilid to be not only effective but superior. The drug can be used in patients who previously would not have been treated with electroconvulsive therapy due to mildness of their illness or physical condition. Marsilid is easy to administer, and no hospitalization is necessary. Patients accept the drug and are not stigmatized. Marsilid is safe, inexpensive, and effective where electroconvulsive therapy fails—especially in repeaters.

CONCLUSIONS

The use of Marsilid produces remarkable improvement in the depressive syndromes because of the drug's antidepressive and psychic energizing properties. Marsilid can energize the patient and yet does not overstimulate him. We have observed improvement in depressed patients regardless of diagnostic category, but, we repeat,[5] Marsilid has little effect on many of the psychotic symptoms that may be present and sometimes increases psychopathologic processes. The tranquilizers are still superior in treating overt psychotic behavior; however, in patients on long-term therapy — twelve to twenty months — discontinuance of Marsilid caused a return of delusions and hallucinations. Apparently, some psychopathology may be alleviated by long-term therapy with a psychic energizer.

We believe our studies during a twenty-month period leave no doubt that Marsilid is a unique anti-depressive or psychic energizer. The Pavlovian theory that depression is a form of inhibition due to excessive stimulation must be seriously questioned.

Considerable doubt remains as to whether Marsilid's inhibition of amine oxidase in the brain is the drug's only essential function. At this time, we are evaluating the energizing action of other amine oxidase inhibitors and psychopharmaceutical agents.

The possible hepatotoxic effects of Marsilid are at present restricting the rational use of this drug by those clinicians who do not look at facts. Marsilid is unique, and no replacement is available. Since Marsilid is used as therapy and as an investigational tool, its loss cannot be evaluated.

Cause of possible toxic action must be determined, whether due to previous liver disease and existing pathology, augmentation of pathologic processes associated with infectious hepatitis, competition with vitamin B_6, chelation and removal of copper from essential oxidative enzyme systems, complex formation with adrenochrome,[11] or unsuspected factors.

The history of science is not simply the history of discoveries and new ideas that tend to approach closer to reality. It is also the history of the defense of these findings against errors due to propaganda, politics, and bureaucracy.

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REFERENCES

1. Loomer, H. P., Saunders, J. C., and Kline, N. S.: Clinical and pharmacodynamic evaluation of iproniazid as psychic energizer. Psychiat. Res. Rep. 8:129, 1958.
2. Beyer, K. H.: Enzymatic inactivation of substituted phenyl-propyl-(sympathomimetic)-amines. J. Pharmacol. & Exper. Therap. 71:151, 1941.
3. Wodraska, T. W., Saunders, J. C., and Kline, N. S.: Combined Ritalin and Serpasil therapy in chronic psychoses. Dis. Nerv. System 19:122, 1958.
4. Philpot, F. J.: Inhibition of adrenalin oxidation by local anaesthetics. J. Physiol. 97:301, 1940.
5. Saunders, J. C., Rochlin, D., Radinger, N., and Kline, N. S.: Iproniazid in depressed and regressed patients. Chapter 32, Psychopharmacology Frontiers, Little, Brown & Co., 1958.
6. Soble, D.: Personal communication.
7. Saunders, J. C.: Etiology of psychosis theorized from drug actions. Chapter 64, Psychopharmacology Frontiers, Little, Brown & Co., 1958.
8. Lewis, A. J.: Manic-Depressive Psychosis, Leopold Bellak, Grune and Stratton, New York City, 1952, p. 243.
9. Vaisberg, M., and Friedland, A.: Personal communication.
10. Bailey, S., and Campbell, H.: Personal communication.
11. Kamijo, K., Koelle, G., and Wagner, H. H.: Modification of effects of sympathomimetic amines and adrenergic nerve stimulation by IIH and INH. J. Pharmacol. & Exper. Therap. 117:213, 1956.

Analeptics: pharmacologic background and clinical use in barbiturate poisoning

Richard K. Richards, M.D.

THE MEANING of "analeptic" is defined here as a drug which restores depressed medullary and cerebral function and removes the consequences of such depression. This paper is about the antagonistic action of such drugs against acute intoxications which occur after ingestion of large doses of barbiturates.

In our discussion of the antagonism between barbiturates and analeptics, we can safely concentrate on a few drugs—pentylenetetrazol (Metrazol), picrotoxin, and bemegride (Megimide). In addition to these drugs, whose clinical-pharmacologic effect is essentially confined to the central nervous system, certain drugs are of importance that are central stimulants as well as sympathomimetics: dextroamphetamine (Dexedrine), d-desoxyephedrine (Desoxyn, Methedrine, and so on) and methylphenidate (Ritalin). Clinical experience and fairly extensive pharmacologic studies indicate that drugs like caffeine, strychnine, camphor, nikethamide (Coramine), and certain others are probably of little, if any, antagonistic value in the treatment of severe barbiturate depression.

PHARMACOLOGIC BACKGROUND

The mode of action of Metrazol and picrotoxin has not been fully explained. However, a great similarity exists between the two which permits us to draw certain tentative conclusions from studies conducted on either drug. The differences in effectiveness of the most potent analeptics on various parts of the supraspinal central nervous system are more of quantity than of quality.

Picrotoxin, a naturally occurring nitrogen-free drug, is the most powerful stimulant of all on a weight or mol basis. Picrotoxin's action is chiefly on the pons and, after large doses, action extends also to the medulla and the spinal cord. When the typical convulsive effect of picrotoxin is elicited, the law of reciprocal innervation is not lost. The depressed respiratory center is directly stimulated—as is the carotid sinus reflex—as a part of the antagonistic effect against barbiturate depression.

While picrotoxin will antagonize the depression of the oxygen consumption caused by barbiturates in whole animals, the drug fails to do so on brain slices in vitro[1,2] or may even cause inhibition of metabolic processes when used in concentrations in vitro corresponding to convulsive doses in vivo.[3] In the motor cortex of the dog, Swank and Cammermeyer[4] have shown that alkaline decreases and an acid phosphatase increases with convulsive doses of picrotoxin.

Many of the actions of picrotoxin are similar to those of Metrazol. Metrazol's convulsive potency decreases after decortication, although the drug also affects the spinal cord. However, the effect on the spine is apparently less pronounced than that of Coramine.[5] This has been confirmed by Hahn and associates[6] and Ten Cate and Swijgman.[7] The work of Guiterez-Noriega[8] apparently indicates that the convulsive action of Metrazol is the result of a summation of a great number of local stimuli arising from sensory and supranuclear mechanisms which augment the direct stimulating effect of the drug on motor neurons.

Esplin[9] has shown that Metrazol greatly enhances polysynaptic and, at higher doses, also monosynaptic activity. Timo-Javia and Werner[10] found that Metrazol and Ritalin affect the posterior thalamus and facilitate impulse transmission in the reticular formation. Jolly

From the Department of Pharmacology, Abbott Laboratories, North Chicago, and Department of Pharmacology, Northwestern University Medical School, Chicago.

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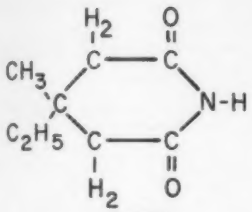

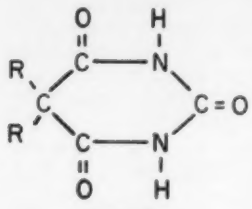

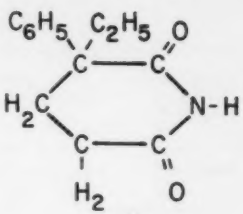

and Steinhaus[11] have observed that Metrazol caused convulsions in lower doses when injected above the midpontine level than below. In work on the isolated cortex, Timo-Javia and Werner[10] found the awakening and convulsive action of Metrazol seemed to come from different levels of the central nervous system. This appears to be in general agreement with the studies of Herken[12] who found that at certain dose levels, hexachlorocyclohexane suppresses the convulsive action of Metrazol without interfering with analeptic activity. Further investigations appear to be highly desirable.

Picrotoxin depresses body temperature, as does Metrazol. Coramine causes temperature increase. If temperature is pathologically lowered by barbiturate intoxication, Metrazol will restore normal conditions as a part of the general analeptic effect rather than as a result of direct stimulation of the thermoregulating center.[13] Other pharmacologically interesting effects of these drugs have been studied by numerous authors.

More recently, a new analeptic drug, Megimide, has been introduced by Shaw.[14,15] This drug has not yet been studied as fully as have picrotoxin and Metrazol. When Megimide was announced, Shaw drew attention to a certain similarity between its structure and that of barbiturates. However, as the illustration shows, a much closer structural relationship exists to the nonbarbiturate, hypnotic glutethimide (Doriden).

Megimide was claimed to possess specific activity against barbiturates and to be, in this respect, different from other analeptics, but most studies indicate this is not the case; for instance, the depression of oxygen consumption of liver mitochondria by barbiturates is not antagonized by Megimide.[16] Our own work[17] has shown that Megimide, under the conditions of the experiments, was not more potent than picrotoxin against barbiturate depression but was more effective than picrotoxin against chloralhydrate. If the dose-effect curves of 3 analeptics, Metrazol, picrotoxin, and Megimide, are compared with 3 different types of depressants, pentobarbital, chloralhydrate, and ethchlorvynol (Placidyl), the slopes of these curves are not much different. The relative potencies of each of the analeptics against the 3 hypnotics are grouped fairly close together.[17] The conclusion then is justified that Megimide is a potent central stimulant and convulsant—probably closer to Metrazol than to picrotoxin—but not strictly a specific barbiturate antagonist.

As measured in anesthetized animals, the relative potency of analeptics apparently depends on the depressant, the species of animals used, and the conditions of the experiments. According to our opinion that analeptics should be used only in severe barbiturate intoxication, the most significant experiments are those studying the effects of analeptic drugs against fatal doses of hypnotic drugs.

Hahn and associates[18] found Megimide the most potent drug against barbital, while, in our studies in mice, picrotoxin and Metrazol have a certain advantage against pentobarbital.[17] In experiments in human beings by Gershon and Shaw,[19] Megimide was found more effective against phenobarbital than against amobarbital or pentobarbital.

Electroencephalographic studies have been used to supplement our knowledge about the direct action of analeptics on the drug-depressed cortex. However, interesting as is the work of Cass,[20] his conclusion regarding the potency and alleged specificity of Megimide

TABLE 1
USE OF ANALEPTICS IN SEVERE BARBITURATE DEPRESSION

Generic name	*Trade name*	*Analeptic usefulness*	*Characteristics*
Picrotoxin*		Very useful	Very potent; cortical effect and safety margin less than Megimide and Metrazol. Long acting. Delayed onset requires careful supervision.
Bemegride*	Megimide	Very useful	Quick acting, very potent, relatively nontoxic, fairly short acting. Needs more study.
Pentylenetetrazol*	Metrazol	Very useful	Quick acting, relatively nontoxic, fairly short duration, very well studied
Phthalic acid bis diethylamide	Neospiran Geastimol	Limited	Good respiratory stimulant, moderate analeptic potency. Depressant component
Nikethamide	Coramine	Very limited	Low toxicity, relatively low effectiveness. Significant depressant component
Caffeine		Very limited	Low potency. Some usefulness as circulatory stimulant
Strychnine		Very limited	Predominantly affecting spinal reflexes
		SYMPATHOMIMETICS	
d–amphetamine	Dexedrine	Limited	In moderate doses helpful in restoring blood pressure. General sympathomimetic actions may become dangerous with high dosage.
d–desoxyephedrine	Desoxyn, Methedrine, and others		
Methylphenidate	Ritalin	Not completely known, probably limited	Similar to Dexedrine, Desoxyn, or Methedrine but less peripheral sympathomimetic action. Safety of very large doses not yet known

*Most effective drugs

as compared with other potent analeptics cannot be accepted; his dose selections had no relation to the drugs' relative toxicity.

In well controlled studies by Hahn and Oberdorf,[21] Megimide and Metrazol proved about equally effective in restoring normal electroencephalographic activity until extremely high doses of barbital were used. Then only Megimide or picrotoxin was still active. Picrotoxin retained a corrective effect upon the depressed blood pressure better than any other drug. However, convulsive electroencephalographic potentials appeared more frequently with picrotoxin than with Megimide. The reviewer doubts that this is a great handicap, providing that picrotoxin is used only during the deepest depression. We have suggested repeatedly that Metrazol or, by inference, probably Megimide, can profitably be administered after some basic analeptic effect has been reached with picrotoxin.[22] Rodin and associates[23] found in human beings that Megimide caused electroencephalographic changes similar to Metrazol but was more potent and produced less subjective symptoms. A direct effect of Metrazol and Ritalin was seen on the electrocorticogram of the isolated cortex preparation after introduction of the drugs into the lateral ventricle as reported by Timo-Javia and Werner.[10]

The purpose of this paper is not to analyze and criticize in detail the very large number of experimental studies concerning the antagonistic-therapeutic value of this group of drugs against barbiturates. While some authors[24] argue against the usefulness of Metrazol in experimental barbiturate poisoning in dogs, their conclusions were to a considerable extent justly criticized by Fazekas and Koppanyi.[25] Depending on the drugs, species used, and the general conditions of the experiments, amounts as high as 3 to 4 times the lethal dose of barbiturates can be successfully antagonized by potent analeptics. This antagonism is reciprocal, but not symmetric; barbiturates detoxify convulsive poisons to a greater extent than convulsive poisons detoxify barbiturates.*

*The paper by Lavenson and associates (*J. Pharmacol. & Exper. Therap.* 122:271, 1958) purports to show that, in cats and dogs poisoned with intravenous pentobarbital, artificial respiration either alone or in combination with Neo-Synephrine is superior in saving lives to analeptics alone. However, no attempts were made to show the effect of the combined use of analeptics, artificial respiration, and vasopressors. Furthermore, all the picrotoxin was given in a single dose, quite different from clinical usage.

CLINICAL USE

In the opinion of the reviewer, analeptic drugs in the treatment of severe barbiturate intoxication are justified and have been extensively, but often not rationally, applied. Drugs used for this purpose are listed in Table 1.

The importance of the use of drugs has sometimes been overemphasized. Often these stimulants have not been handled with the skill and caution which their powerful properties require. On the other hand, experts in the field have repeatedly emphasized that restoration and maintenance of adequate oxygenation, proper fluid balance, and meticulous general care form the indispensable basis of any treatment of central depression. In recent years, a determined drive against the use of analeptic drugs and for supportive treatment alone spearheaded by Nilsson[26] and other Scandinavian authors has found enthusiastic followers in this country.

We cannot discuss all the pros and cons of this controversy. Hahn[27,28] and associates in Germany, Koppanyi and Fazekas,[29] this author,[22] and others in this country believe that certain analeptics have a place in the management of extreme barbiturate intoxication.

In analyzing some of the objections raised by Nilsson[26] and others against the use of analeptic drugs, there is no question that Nilsson's work has correctly emphasized the need for supportive therapy, and he deserves great credit for improvement in general care. Incidence of death among Nilsson's patients has dropped significantly. However, analysis of his cases indicates that the majority of his patients did not belong to the most severe type; many of them had Alurate poisoning, a relatively low-potent and not long-acting barbiturate. Particularly disconcerting for the critical reader is the fact that Nilsson uses for comparison in his own experience patients treated with Coramine and Geastimol—also called Neospiran in Germany.

Geastimol is not available in the United States but was studied experimentally by this author a number of years ago.[31] The drug was rejected because, like Coramine, the antagonistic effect in severe barbiturate poisoning was low and it also possessed a depressant component. Nilsson does not indicate that he has studied Metrazol or picrotoxin to any extent, and, apparently unaware of the significant experimental and clinical differences between certain groups of analeptic drugs, he comes to unjustified generalizations.

Some of the most important work on the effect of convulsants—the publication by Schmidt and associates[32]—is often quoted as proof that drugs like picrotoxin would increase the oxygen need of the brain enormously and thus contribute to brain anoxia. Actually, Schmidt's work refers to production of convulsions by picrotoxin or Metrazol. No evidence is found that analeptics increase the oxygen consumption of the brain in nonconvulsive doses beyond the capacity of oxygen supply. Furthermore, the oxygen need of the barbiturate-depressed brain is actually lowered. In fact, Schmidt's data show that in 1 deeply depressed monkey, a therapeutic dose of picrotoxin restored corneal reflex, lightened depression, and raised cerebral blood flow and oxygen consumption to normal values.

In extreme experimental respiratory depression caused by barbiturates, both Metrazol and picrotoxin significantly increase oxygen saturation of the blood and produce a fall of CO_2 levels.[33] As Nilsson states in referring to previous studies by various authors, certain analeptics also possess a depressing component; this applies much more to coramine and Geastimol than to Metrazol and picrotoxin. Even as conservative an investigator as Eckenhoff[34] stated that clinical experience absolves Metrazol and picrotoxin from secondary depressing effects when given to human beings in nonconvulsive doses. This author, as well as Hahn,[27] agree with this interpretation.

Megimide is an analeptic—probably closer to Metrazol than to picrotoxin—but with essentially similar action in most aspects of pharmacodynamics. Originally, Megimide was thought not to be convulsive when given in high doses. However, this has been disproved. Similarly, the claim by Achor and associates[35] that Megimide changes the distribution of barbiturates in the body should be confirmed. Previous well controlled work with other analeptics[1,36] has failed to show such an effect.

At this time, many papers about Megimide are appearing with the enthusiasm common to the appearance of a new drug. Scandinavian authors, who often display a negative attitude

TABLE 2

Symptoms of severe barbiturate poisoning	Coma, no response to painful stimuli. Reflexes extremely depressed or absent. Varying degrees of respiratory depression. Condition not significantly changed after initial care
General restorative and supportive measures	Provide free airway, prevent atelectasis. Oxygen is indicated. Artificial respiration when needed. Diminish absorption of drug by gastric lavage in early cases. Encourage excretion by laxation—Na-phosphate or sulfate—and diuresis. Maintain fluid and mineral balance. Blood dialysis if available and when indicated. Prevent and treat shock. Administer vitamins, especially in prolonged coma.
Supportive drug treatment	Antibiotics and pressor agents—Neo-Synephrine, Levophed—when needed. Others as indicated
Analeptics	(Opinion divided): Picrotoxin—the most potent in deep depression—Metrazol or Megimide. Use only to lighten coma until reflexes return. Reduce dose for maintenance. Do not try to force awakening because of the danger of convulsions. Sympathomimetics are permissible in moderate doses but may cause circulatory overstimulation.

to this class of drugs, are now impressed with the stimulating action of Megimide.[37] This effect is probably particularly remarkable to them as, judging from the literature, Metrazol and picrotoxin have not been well studied there. This is also evident from the statement of Louw[37] that "the preparation [Megimide] has the advantage over central analeptics previously employed in that it does not cause overloading of the heart by increase in blood pressure nor hyperpyrexia." However, with the correct use of Metrazol or picrotoxin, circulatory complications occur rarely, if at all.

Evidence has not yet proved that Megimide is significantly different. In recent studies,[38] the effect of Megimide on temperature regulation has been shown to be essentially the same as that of Metrazol. Apparently, Megimide is a useful analeptic somewhat more powerful than Metrazol and less so than picrotoxin, with a greater margin of safety than either.

Comparison of mortality figures between patients treated with and without analeptics is thoroughly unsatisfactory; well controlled, sufficiently large studies within the same institution and with analeptics as the only variable, are not available at the present time.

It cannot be emphasized enough that those who recommend the rational use of analeptics stress the need for all supportive measures and want the administration of such drugs restricted to extreme intoxications. No attempt should be made to arouse such patients but only to stimulate them until vital reflexes and some spontaneous activity are restored, thus avoiding convulsions. This result can be obtained quite safely in many patients by the intelligent use of drugs like picrotoxin, Metrazol, and Megimide.

The low organ toxicity of picrotoxin and Metrazol is truly astounding. Doses as high as 14 gm. of picrotoxin or 17 gm.—and even 25.9 gm.—of Metrazol have been successfully given for a few days to patients with barbiturate intoxication without producing sequelae. Present indications are that Megimide will have the same properties. Who will seriously deny that we render a service to a patient by reducing the period of deep coma from several days to a few hours? Furthermore, the reduction of the need for prolonged nursing cannot be disregarded in face of the scarcity of trained personnel in many hospitals. The two opposing views have just recently been restated by Eckenhoff and Dam[39] for the conservative treatment and by Koppanyi and Richards[40] for the judicious use of analeptics.

Certain of the sympathomimetic amines have found some favor in the treatment of barbiturate poisoning. While these drugs have considerable analeptic potency, their stimulating effect upon the circulatory system, especially with high and repeated doses, is not without danger—particularly in the older patient. Furthermore, in higher doses, sympathomimetic amines may have a depressant component. In our experience, moderate amounts of these drugs are useful in restoring a drop in blood pressure. However, in severe vascular collapse, plasma expanders and drugs like Neo-Synephrine or norepinephrine (Levophed) must be used; these, in turn, are free of cen-

tral stimulating action. However, no specific antagonist against barbiturates or other hypnotics exists. Probably, the range of usefulness of potent analeptics will also apply more or less to the new nonbarbiturate hypnotics such as Doriden, Noludar, Valmid, and Placidyl.

More recently, analeptic drugs have been tried as a means to awaken patients from barbiturate anesthesia or to shorten recovery. That this is possible in principle and within limits had been shown several years ago with Metrazol.[41] Ritalin and Megimide are now being studied. The results are not uniform, and the usefulness of this procedure is not yet definitely established.

Table 2 shows in schematic form a treatment schedule for extreme barbiturate intoxication. Some of the more recent and promising procedures, such as hemodialysis, are mentioned but not discussed in detail.

REFERENCES

1. Goldbaum, L. R., and Hubbard, T. F.: Effects of picrotoxin on thiopental metabolism and on in vitro respiration of brain tissue in mice. Anesthesiology 11: 733, 1950.
2. Krantz, J. C., Carr, C. J., and Beck, F. F.: Further study of barbiturate-picrotoxin antagonism. J. Pharmacol. & Exper. Therap. 61:153, 1937.
3. Klein, J. R.: Inhibition of brain respiration by picrotoxin. J. Biol. Chem. 151:651, 1943.
4. Swank, R. L., and Cammermeyer, J.: Selective effect of anesthetics and picrotoxin on cerebral cortex of the dog: electro-encephalographic and histochemical study. J. Cell. & Comp. Physiol. 34:43, 1949.
5. Kohn, R., and Jacobi, M.: Untersuchungen über qualitative und quantitative Beziehungen zwischen Schlafmitteln und Analepticis. Arch. f. exper. Path. u. Pharmakol. 179:448, 1935.
6. Hahn, F.: Untersuchungen über die Angriffspunkte von Cardiazol und Coramin. Arch. f. exper. Path. u. Pharmakol. 205:552, 1948.
7. Ten Cate, J., and Swijgman, D. W.: Localisation des origine des convulsions produites par le cardiazol et la coramine. Arch. internat. pharmacodyn. 70:293, 1945.
8. Guiterrez-Noriega, C.: Action of Metrazol on motor and sensory nuclei of brainstem. J. Neuropath. & Exper. Neurol. 2:132, 1943.
9. Esplin, D. W., and Curto, E. M.: Effects of trimethadione on synaptic transmission in spinal cord. J. Pharmacol. & Exper. Therap. 121:457, 1957.
10. Timo-Jaria, C., and Werner, G.: Electroencephalographic changes caused by some analeptic drugs. Arch. internat. pharmacodyn. 112:451, 1957.
11. Jolly, E. R., and Steinhaus, J. E.: Effect of drugs injected into limited portions of cerebral circulation. J. Pharmacol. & Exper. Therap. 116:273, 1956.
12. Hefken, H.: Eingriffe am Nervensystem mit Hexachlorcyklohexan. Arzneimittel-Forsch. 1:356, 1951.
13. Hahn, F.: Ueber den Einfluss einiger Analeptica (Cardiazol, Coramin, Neospiran und Cycliton) auf die Körpertemperatur des normalen und narkotisierten Kaninchens. Arch. f. exper. Path. u. Pharmakol. 202: 165, 1943.
14. Shaw, F. H., Simon, S. E., Cass, N. M., and Shulman, A.: Barbiturate antagonism. Nature 174:402, 1954.
15. Shulman, A., Shaw, F. H., Cass, N. M., and Whyte, H. M.: New treatment of barbiturate intoxication. Brit. M. J. 1:1238, 1955.
16. Jalling, O.: Effect of β,β-methylethyl glutarimide and amytal on rat-liver mitochondrial respiration. Nature 177:330, 1956.
17. Kimura, E. T., and Richards, R. K.: A comparative study of bemegride (β,β-methylethyl glutarimide; NP-13, Megimide) as analeptic in mice. Arch. internat. pharmacodyn. 110:29, 1957.
18. Hahn, F., and Schunk, R.: Zur Behandlung der Schlafmittedvergiftung mit Analeptika; ein experimenteller Ueberblick mit besonderer Berücksichtigung des Methyläthylglutarimid (Megimide, Eukraton). Deutsche med. Wchnschr. 8:1643, 1956.
19. Gershon, S., and Shaw, F. H.: Effects of bemegride on barbiturate overdosage in humans. Brit. M. J. 2:1509, 1957.
20. Cass, N. M.: An EEG study of analeptic action of β,β-ethylmethyl glutarimide (Megimide). Brit. J. Anaesth. 28:325, 1956.
21. Hahn, F., and Oberdorf, A.: Vergleichende Versuche mit β-methyl-β-athyl-glutarimide, Pentamethylenetetrazol und Pikrotoxin am EEG und Blutdruck der Katze. Arch. f. exper. Path. u. Pharmakol. 231: 298, 1957.
22. Richards, R. K., in Kyser, F. A.: Therapeutics in Internal Medicine. New York City, Paul B. Hoeber, 1953, pp. 622-627.
23. Rodin, E. A., Rutledge, L. T., and Calhoun, H. D.: Megimide and Metrazol (A comparison of their convulsant action in mice and the cat). Electroencephalog. & Clin. Neurophysiol. 10:208, 1958.
24. Bailey, H. A., Goth, A., and Lackey, R. W.: Reevaluation of metrazol in barbiturate poisoning. Anesth. & Analg. 32:274, 1953.
25. Fazekas, J. F., and Koppanyi, T.: Evaluation of pentylenetrazol as barbiturate antagonist. Anesth. & Analg. 33:58, 1954.
26. Nilsson, E.: On treatment of barbiturate poisoning. Acta med. scandinav. 139:1, 1951, supp. 253.
27. Hahn, F.: Ueber nützliche und schädliche Wirkungen der Analeptica bei der Schlafmittelvergiftung. Klin. Wchnschr. 32:925, 1954.
28. Hahn, F.: Pharmakologie und Toxikologie der Schlafmittel. Deutsches med. J. 6:293, 1955.
29. Koppanyi, T., and Fazekas, J. F.: Pharmacotherapeutic nihilism in treatment of acute barbiturate poisoning. Am. J. M. Sc. 224:577, 1952.
30. Richards, R. K., and Koppanyi, T.: Barbiturate intoxication. J.A.M.A. 154:438, 1954.
31. Richards, R. K.: Unpublished studies on pharmacology of Neospiran, 1936.
32. Schmidt, C. F., Kety, S. S., and Pennes, H. H.: Gaseous metabolism of brain of monkey. Am. J. Physiol. 143:33, 1945.
33. Anderson, W. R., and Teague, R. S.: Effect of analeptics on arterial blood gases of dogs during barbiturate anesthesia. J. Pharmacol. & Exper. Therap. 118: 368, 1956.
34. Eckenhoff, J. E.: A status report on analeptics. J.A.M.A. 139:780, 1949.
35. Achor, L. B., Geiling, E. M. K., and Domek, N. S.: Alteration of pentothal-S^{35} distribution in mice by single doses of methyl-ethyl-glutarimide (NP-13). Anesth. & Analg. 35:534, 1956.
36. Kahn, J. B., Jr.: Effects of picrotoxin on distribution and excretion of C^{14}-labeled pentobarbital. Anesth. & Analg. 31:130, 1952.
37. Louw, A.: Treatment of acute barbiturate acid poisoning. Danish M. Bull. 5:137, 1958.
38. Hahn, F.: Personal communication.
39. Eckenhoff, J. E., and Dam, W.: Treatment of barbiturate poisoning with or without analeptics. Anesth. & Analg. 37:174, 1958.
40. Koppanyi, T., and Richards, R. K.: Treatment of barbiturate poisoning with or without analeptics. Anesth. & Analg. 37:184, 1958.
41. Pickrell, K. L., and Richards, R. K.: Pentothal-Metrazol antagonism: method of shortening recovery period following Pentothal anesthesia. Ann. Surg. 121:495, 1945.

Modification of Metrazol-induced convulsions by ablations of the brain

A study in the salamander

J. J. Peters, Ph.D., A. R. Vonderahe, M.D., and
K. N. Hehman, B.S.

IF CERTAIN TYPES of living activity take place after the ablation of an organ, then that organ is not required for this activity and the cause lies in remaining structures. In the present investigation, this often used method of localizing biologic functions has been applied to the salamander to provide a clearer correlation between structure and function for such convulsionary phenomena as sudden onset, tonic and clonic phases, hypersensitivity, gasping, and writhing. From several points of view, the salamander is a favorable subject for this type of experimentation. The anatomy of the salamander's brain, which has been described by Herrick[1] as being longitudinally extended and easily accessible, is less complex than that of mammals. Ablation produces almost no shock in the salamander. Furthermore, since convulsions can be induced and modified by use of the same chemical and electrical agents in salamanders[2,3] and mammals, including man,[4] the biologic mechanism has fundamental similarity and there is some hope that the data provided by studying the salamander may supply clues for clearer understanding of convulsionary phenomena in higher forms.

MATERIAL AND METHODS

About 60 adult salamanders, the aquatic phase of Triturus viridescens, were used in this study. The ablations were designed to test the influence of 5 major embryologic divisions of the central nervous system—telencephalon, diencephalon, mesencephalon, rhombencephalon, and spinal cord—on induced seizures. Fundamentally, the same results were observed after 3 different operations—cauterization, transection with a small rotary saw, and simple removal of portions of the brain with a fine jeweler's forceps. Neurologic tests done five or ten minutes after ablation were designed[5] to determine the function of various pathways in the nervous system and consisted of responses to touch; corneal and abdominal reflexes; walking, righting, and swimming; and a visual response to black and white bars on a moving drum. Metrazol, 3 mg. per gram of body weight, was injected into the abdominal cavity, with a few drops applied to the region of ablation. During the next thirty minutes, the reaction of the salamander to Metrazol was compared with that of an intact salamander undergoing a characteristic seizure, including clonic and tonic phases, as described by Peters and Vonderahe.[2] The salamander then was fixed in 10% formalin for subsequent dissection and sectioning to determine the actual extent of the ablation.

RESULTS

Behavior of untreated salamanders after ablations. The modification of behavior by successively larger ablations in different salamanders is summarized in Figure 1, which is based on the results of the neurologic tests.

After ablation of the telencephalon, the salamander has coordinated walking, swimming, and righting; corneal and abdominal reflexes; a positive reaction to tactile stimulation; and the visual response. Although coordinated, walking is rendered abnormal by hyperextension of the forelimbs.

Ablations of the prosencephalon and mid-

From the Albers Biological Laboratory, Xavier University, Cincinnati, and the Department of Anatomy, College of Medicine, University of Cincinnati.

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brain cause loss of hyperextension of forelimbs and visual response. However, the salamander retains the ability to walk, swim, and right itself; furthermore, the limbs are withdrawn in response to tactile stimulation and an abdominal reflex is apparent.

When ablation is extended to include the hindbrain, all the responses mentioned above are lost, except the abdominal reflex and withdrawal of limbs after touching.

Modification of induced seizures by ablations. The effect of successively larger ablations on various convulsive phenomena as observed in different salamanders is summarized in Figure 2.

After ablation of the telencephalon, the salamander has a Metrazol-induced seizure similar to that of an intact animal. Onset is sudden and violent, with definite clonic and tonic phases, gasping, writhing, and hypersensitivity to tactile stimulation. In some instances, ablation of the telencephalon seems to intensify the violence of the seizure.

After ablation of the forebrain, sudden onset, clonic phenomena, and hypersensitivity to tactile stimulation are not apparent. However, the animal gasps, writhes, and has a tonic phase that generally is more extreme and prolonged than that of intact salamanders.

When both the prosencephalon and mesencephalon are removed, injection of Metrazol causes conspicuous writhing along the vertebral column, repeated placement and withdrawal of limbs, and gasping. However, no definite tonic phase, clonus, or hypersensitivity is noted.

After ablation of the entire brain, including the rhombencephalon, and injection of Metrazol, behavior of the salamander is similar to that observed after both the prosencephalon and mesencephalon are removed, except that gasping disappears and writhing and repeated placement of limbs are less intense.

DISCUSSION

The results of this investigation add further support to the view that, during phylogenetic and ontogenetic development, the higher centers of the central nervous system do not replace the functions of lower centers but rather successively superimpose on them a more refined regulatory control. As ablations proceed

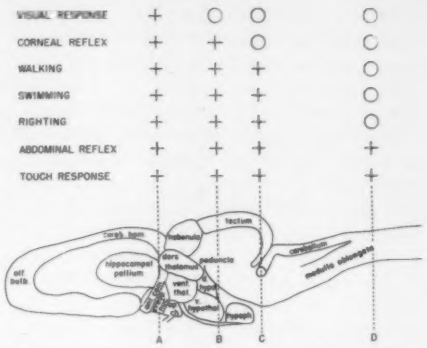

Fig. 1. Diagram of the medial aspect of the brain of the salamander and modifications of behavior by successively larger ablations indicated by the vertical lines at levels A, B, C, and D. The plus signs indicate the presence and zeros the absence of responses. When the transection is at level A, all responses are present; the visual response is absent at B; the corneal reflex is absent at C; and only the abdominal reflex and response to touch remain at D.

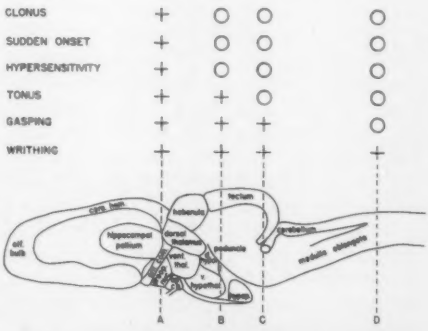

Fig. 2. Diagram of the medial aspect of the brain of the salamander and modifications of convulsive phenomena by successively larger ablations indicated by the vertical lines at levels A, B, C, and D. The plus signs indicate the presence and zeros the absence of phenomena. When the transection is at level A, all components are present; clonus and hypersensitivity are absent at B; a definite tonic phase is absent at C; and only writhing and erratic placement of limbs remain at D.

posteriorly, eliminating the higher centers, the salamander has successive deficiencies in such refined actions as walking, righting, and swimming until only gross writhing of the vertebral column remains. The most posterior ablations reduce the responses of an adult salamander to what Coghill[6] or Herrick[1] might call a "total pattern" of behavior similar to that of an early embryo and devoid of all the "local patterns" later acquired with the development of higher centers. The experimental results of this study seem to establish the following hierarchy of control: Writhing is the basic movement on which a placement of limbs is superimposed. A motor zone in the medulla marshalls these simple movements into acts of swimming, walking, and righting. Finally, the midbrain and forebrain, with centers for sensory correlation, integrate these activities to move and adjust the organism to environmental changes.[7]

Successively larger ablations followed by injections of Metrazol produce effects that suggest the presence of several components in the physiology of walking, with centers for control in different parts of the central nervous system. The erratic placement of limbs in a spinal salamander resting on its belly without actually walking suggests the presence of a progressive component that is responsible for forward movement. This component is brought into action by a stimulation of the spinal mechanism. However, the inability of the spinal salamander to stand or actually walk postulates the existence of another or postural component to overcome gravity. Control centers for such an antigravity component probably are located in the rhombencephalon, since the salamander walks coordinately, even after a removal of the forebrain and midbrain. The hyperextension of forelimbs when only the telencephalon is ablated suggests that the telencephalon exerts a controlling inhibitory influence on the postural component. These comments find agreement with Langworthy's[8] observation that progression in pigeons and mammals appears as a fundamental activity of the spinal cord, while posture is controlled by the brain. It is noteworthy that, even in the intact salamander, Metrazol exerts a differential effect on the several components of walking, especially after the seizure. Metrazol allows the placement of limbs, although erratic, to continue but impedes the postural component so that the animal tends to lie on its belly.

A cerebral cortex may participate in the tonic and clonic phases of a seizure,[9] but the results of this investigation dispute the generalization that a cerebral cortex is required for all convulsions with tonic or clonic components. The brain of the salamander has no cerebral cortex,[1] and, yet, the salamander undergoes conspicuous clonic and tonic phases during induced convulsions, even when part of the telencephalon is excised.

The striatum, diencephalon, or both may be responsible for clonus, sudden and violent onset, and hypersensitivity, since ablation of these structures in the salamander abolishes clonic activity, sudden onset of seizure, and hypersensitivity.

Persistence of a tonic phase with atypical severity after ablation of the forebrain permits 2 conclusions: [1] The midbrain contains mechanisms adequate for the production of a tonic phase and [2] the extreme severity of the tonic phase implies release from the regulatory control of higher centers coordinating sensory input to adjust the organism to a changing environment. A similar opinion was held by Langworthy,[10] who stated that transection of the brain stem at the level of the midbrain frees the tonic mechanism from inhibitory control. Ueda[11] described some twitching in dogs after a removal of the midbrain and administration of Metrazol; this twitching may correspond to the writhing mentioned in this report and not strictly to clonic activity.

Since walking, swimming, righting, and gasping during seizures persist until the rhombencephalon is removed, motor centers for these activities apparently reside in the hindbrain. However, ablation of regions of the brain anterior to the hind-brain coincides with an absence of both clonic and tonic phases. These results are at variance with the view that tonic and clonic phases can be evoked by the presence and stimulation of any motor center.[12]

The production of an opisthotonoid posture and clonic activity of the trunk is obvious evidence that the spinal cord participates in both tonic and clonic phases of a seizure.

However, much of this participation is due to the fact that impulses originate in the brain, as indicated by the disappearance of tonic and clonic activity from the trunk when the spinal cord is separated from the brain. Results of the ablations indicate that writhing and placement are due to mechanisms located in the spinal cord and brought into increased activity by Metrazol. Different mechanisms in the spinal cord are exposed by the differential action of such convulsant drugs as Metrazol, strychnine, and nicotine. In a salamander with a transected cord, Metrazol produces a series of successive impulses moving along the vertebral column and culminating in writhing; strychnine provokes a periodic, generalized, spastic jerk of the trunk; and nicotine evokes local ripples of muscle along the vertebral column.[13]

Although Metrazol generally is regarded as an excitatory drug, the present investigation reveals it to be a suppressor. The salamander can walk, right itself, and swim, even after an ablation of the brain anterior to the rhombencephalon. With the convulsant action of Metrazol, these activities disappear, leaving only gasping and writhing. These data suggest that the lack of walking, righting, or swimming after a seizure is due not to the action of the drug on higher centers, which are absent after ablation, but to an inhibitory effect on some region posterior to the transection, probably the cerebellum or motor centers in the medulla.

SUMMARY

1. After ablation of the telencephalon, the salamander has coordinated walking, righting, and swimming; corneal and abdominal reflexes; and positive responses to tactile and visual stimulation. Intraabdominal injection of Metrazol induces seizures with tonic and clonic components, hypersensitivity, gasping, and writhing.

2. After ablation of the prosencephalon, Metrazol induces a seizure with an extreme, tonic phase but hypersensitivity and the clonic phase are lost.

3. When both the prosencephalon and mesencephalon are removed, the salamander still walks, rights itself, and swims but Metrazol fails to evoke seizures with tonic and clonic components.

4. The salamander still has an abdominal reflex and withdraws the limbs when touched after the entire brain is excised, but injection of Metrazol is followed mainly by writhing and erratic placement of limbs.

5. The relationship of these observations to some aspects of phylogenetic development and to walking, localization of some seizure phenomena, and the mode of action of Metrazol is discussed.

REFERENCES

1. Herrick, C. J.: The Brain of the Tiger Salamander. University of Chicago Press, Chicago, 1948.
2. Peters, J. J., and Vonderahe, A. R.: Electroencephalographic studies, induced seizures and their modification by phenobarbital, dilantin and phenurone, in the salamanders, Triturus viridescens and Ambystoma tigrinum. EEG Clin. Neurophysiol. 6:253, 1954.
3. Peters, J. J., and Vonderahe, A. R.: Effect of themisone and phenurone on electrically-induced seizures in the salamander. Neurology 3:890, 1953.
4. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics. The Macmillan Co., New York, 1955.
5. Peters, J. J., Vonderahe, A. R., and Palmisano, P. A.: A use of the salamander for investigating and testing the anticonvulsant properties of drugs. J. Pharmacol. & Exper. Therap. 118:90, 1956.
6. Coghill, G. E.: Correlated anatomical nad physiological studies of the nervous system of amphibia. V. The growth of the pattern of the motor mechanism of Ambystoma punctatum. J. Comp. Neurol. 40:47, 1926.
7. Detwiler, S. R.: Experiments upon the midbrain of Ambystoma embryos. Am. J. Anat. 78:115, 1946.
8. Langworthy, O. R.: Abnormalities of posture and progression in the pigeon following experimental lesions of the brain. Am. J. Physiol. 78:34, 1926.
9. Dandy, W. S.: Experimental investigations on convulsions. J.A.M.A. 88:90, 1927.
10. Langworthy, O. R.: The control of tonus after injuries to the brain and spinal cord of man. Medicine 11:225, 1932.
11. Ueda, T.: An interruption of experimental convulsion with special aspect on midbrain. Osaka Daigaku Igaku Zassi. 3:13, 1951.
12. Hori, V.: Experimental studies on the convulsions viewed from the isoelectrical point of cells in the brain centers. Osaka Daigaku Igaku Zassi 5:147, 1951.
13. Peters, J. J., Vonderahe, A. R., and Powers, T. H.: Comparative effects of some convulsant drugs on the behavior and electrical activity of the nervous and muscular system of the salamander. J. Pharmacol. & Exper. Therap. 123:28, 1958.

Improved method of obtaining biopsies of neuromuscular junction in man

Oscillographic delimitation of end plate on exposed muscle

C. Coërs, M.D.,* and J. E. Desmedt, M.D.

ALTHOUGH USED BY DUCHENNE as early as 1872,[1] muscle biopsies have only recently become part of current neurologic investigations. In order to be really informative, the excised specimens should obviously include not only muscle tissue, but neuromuscular junctions as well. This requirement can be achieved by taking the biopsy at the motor point, as defined by electrical stimulation first on the skin, then on the exposed muscle.[2] Such a procedure does not entail any paralysis of the concerned muscle, since only terminal nerve fibers innervating the most superficial bundles are severed, and the lesion does not reach the motor nerve trunk which enters the muscle by its deep aspect.

The method described in this paper involves recording, directly from the exposed muscle, action potentials evoked by nerve stimulation. As will be shown, it is possible by this method to delimit very accurately the end plate zone which can thus be excised, if necessary, with a minimal amount of surrounding muscle tissue. Such neuromuscular biopsies of minimal size are required for electron microscopy. Another advantage of the electrical recording is that functional defects can be assessed[3] on the very muscle samples taken for the histopathologic study. It is well known that wide variations occur in the degree of involvement of individual muscles in neuromuscular diseases. Sometimes even the morbid process affects only certain muscles of the body. Valid correlations can thus be established only if both the morphologic and functional tests are applied on the same muscle in a given patient.

As far as we are aware, such combined study has not yet been made at the level of the neuromuscular junction in man. It should be mentioned, however, that a few electromyographic studies with the concentric electrode have already benefited from anatomic checks on excised specimens of muscle tissue.[4,5]

OSCILLOGRAPHIC DELIMITATION OF END PLATE REGION

Good evidence exists that the end plate region is located at about equal distances from either tendon insertions of the corresponding muscle fiber.[6] The muscle action potential evoked by the motor nerve thus proceeds necessarily from this central region toward both ends. The focus of the spike can be located according to the polarity of the electrical sign recorded with bipolar electrodes.[7] The procedure is basically similar to the one currently used in electroencephalography to localize a focus of activity in the brain.[8,9]

The manner of connecting the recording leads to the input of the balanced amplifier is obviously essential for consistent results. The convention adopted throughout this paper is to represent by a solid line the lead which produces an upward deflection of the oscilloscope trace when it becomes electronegative with respect to the other lead. The latter is represented by a broken line.

When a single, maximal shock is delivered to the motor nerve, action potential is initiated in the muscle membrane close to the end plate—as sketched in Figure 1A. At this early stage, electrode 2, which is supposed to be close to the junctional region, becomes electro-

From the Laboratoire de Pathologie générale, University of Brussels, Belgium. This work was supported in part by the Rockefeller Foundation and by the Muscular Dystrophy Association of America, Inc.

*Service de Médecine interne, Département de Neurologie, Hôpital Brugmann, Brussels.

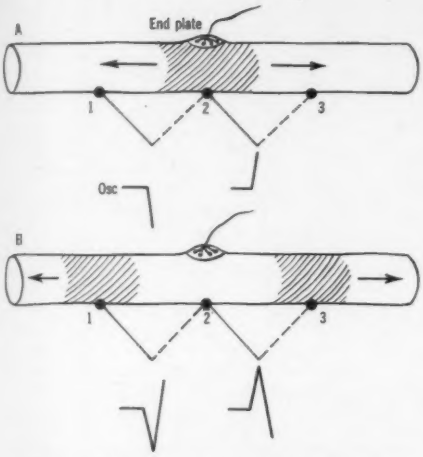

Fig. 1. Diagram of a muscle fiber in the course of neuromuscular activation. The area of the fiber membrane invaded by the muscle spike is indicated by hatching. Osc = oscillograms supposed to be recorded with the electrodes connected as indicated (see convention for connection of leads in text.) *(A)* Early stage of neuromuscular activation. *(B)* Later stage in which the muscle spike propagates from end plate region toward both tendon ends.

negative with respect to electrodes 1 and 3 which are placed somewhat further along the muscle fiber. Therefore, if electrodes 1 and 2 are connected to the amplifier—as indicated in the diagram—a downward deflection is recorded. With electrodes 2 and 3 similarly connected, an upward deflection is seen. The initial potential change evoked by the nerve shock thus reverses its polarity when the bipolar exploring electrodes pass across the end plate. Somewhat later in the same sequence of events, the action potential wave has left the junctional region and propagates along the muscle fiber (Fig. 1B). At that stage, electrodes 1 and 3 are negative with respect to electrode 2. The oscilloscope traces are consequently driven in the opposite direction, giving the diphasic appearance of the recorded spike.

As an illustration of the localization principle, actual records obtained from the cat's gracilis muscle are presented in Figure 2. In this experiment, instead of a pair of bipolar electrodes which have to be swept along the muscle surface, we use an array of 10 electrodes fixed in a Plexiglas holder at 1 mm. distance from each other. Any 2 of these electrodes can be connected in turn to the amplifier input without moving the array while exploring the end plate region. The polarity of the first potential change evoked by an indirect shock is downwards in A and B and upwards in C and D. This is taken to indicate that the focus of initiation of the muscle spike is near electrode 3, as can be easily proved by injecting a full dose of d-tubocurarine into the cat's

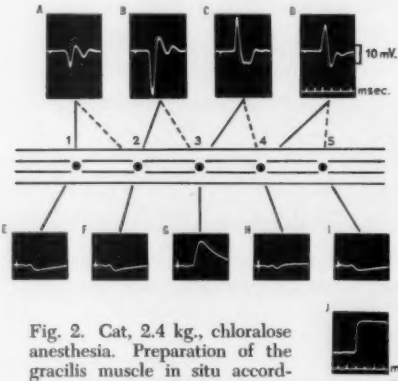

Fig. 2. Cat, 2.4 kg., chloralose anesthesia. Preparation of the gracilis muscle in situ according to Brown and Burns.[10,7] Temperature of the paraffin pool overlying the exposed muscle, 36.5° C.; rectal temperature, 37.5° C. Each tracing represents a cathode-ray oscillogram of the response evoked in the muscle by a single maximal shock on the motor nerve. A, B, C, and D are responses recorded with bipolar electrodes before curarization. The polarity of the first deflection of the muscle spike clearly reverses on electrode 3. The amplitude of the wave is different in the 4 records, but this fact is not very significant since the bipolar recording electrodes are only separated by 1 mm. and distort the action potential. E, F, G, H, and I are responses recorded in completely curarized muscle. The same electrode array is used but connected monopolarly to the amplifier to avoid distortion of the end plate potential. An indifferent electrode is placed on the tendon end. It is observed that an end plate potential—negative upwards—only appears on electrode 3. The small positive waves seen in records E, F, H, and I are due to a volume-conductor effect. J is 1 mv. calibration step and time in milliseconds for the series of records E to I.

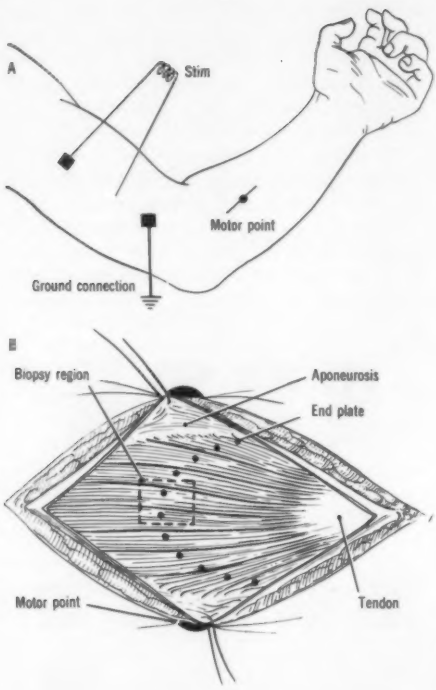

Fig. 3. Diagrams showing procedure used in taking neuromuscular biopsies of flexor carpi radialis muscle. *(A)* Stim = stimulator output connected to needle (distal) and skin electrodes used to excite the median nerve. The longitudinal line traversing the motor point of flexor carpi radialis represents the incision performed to expose the muscle. *(B)* Operating field after the aponeurosis has been incised and retracted. Motor point previously determined on the skin is supposedly split in 2 half circles by the skin incision. Fiber bundles are seen converging on the tendon, and the black dots indicate approximate location of end plates. The diagram represents a much more extensive exposure of the muscle surface than is actually performed. With the usual incision, such as illustrated in A, only the motor end plate zone indicated by the interrupted line is seen.

vein to block neuromuscular transmission. The motor nerve impulse then only evokes a subthreshold end plate potential which is the local electrical sign of the transmitter action.[11,12] In the lower row of records in Figure 2, the same electrodes are still in the same position along the muscle surface and are connected monopolarly to the amplifier—an indifferent electrode being placed on the tendon end. An end plate potential of about 0.8 mv. appears on electrode 3 (Fig. 2G) which had been identified as lying nearest to the focus of initiation of the muscle spike before the animal was curarized. This is good evidence for the consistency of the localization method.[7]

CHOICE OF A SUITABLE MUSCLE

Muscles are not equally suitable for taking neuromuscular biopsies, and the following requirements have to be satisfied:

1] The muscle should be superficial to avoid extensive dissections.

2] The muscle should be large enough to prevent impairment of function by excision. Small muscles of face, hand, and foot should not be used.

3] Muscle fibers should run uninterruptedly from origin to insertion in parallel bundles—so that their end plates are grouped in a well delimited transverse innervation band. Muscles attaching themselves on extensive bony and aponeurotic surfaces such as tibialis anticus and brachioradialis are not very suitable in this respect.

These 3 requirements are fulfilled by the following muscles which have been used in biopsy studies:[6] sternocleidomastoideus, deltoideus, biceps brachii, palmaris longus, flexor carpi radialis, vastus medialis, and peroneus brevis. In the present study is a fourth requirement—the motor nerve should be easily accessible for stimulation—a condition which eliminates proximally situated muscles such as deltoideus.

Until now, we have used the flexor carpi radialis and palmaris longus, which proved to be very convenient. Vastus medialis and peroneus brevis would also lend themselves easily to the procedure.

PROCEDURE USED FOR FLEXOR CARPI RADIALIS

The patient is comfortably seated in an armchair with the left arm attached in a semi-

Fig. 4. Pattern of terminal motor innervation in flexor carpi radialis muscle. Transverse section in a plane parallel to the overlying skin. The specimen was taken at autopsy from a 3-month-old child. The cholinesterase of the subneural apparatuses is selectively stained with a modified Koelle method;[13,6] End plates appear neatly concentrated in an innervation band running at equal distance between the muscle fiber insertions. The portion of the muscle which is investigated and excised in the present study corresponds to the axial bundles.

flexed, supinated position. No general anesthesia or premedication is given.

1] **Electrode for nerve stimulation.** A steel needle 0.3 mm. in diameter is inserted through the skin so that the tip is close to the trunk of the median nerve, at the level of the distal third of the arm (Fig. 3). A small metal plate smeared with electrode paste is fixed more proximally on the skin. Both electrodes are connected to the output of a Grass stimulator so that supramaximal cathodal pulses of 0.1 msec. duration can be delivered to the nerve later in the experiment. Another electrode placed near the elbow serves to ground the patient.

2] **Check of muscle temperature.** A needle thermocouple is inserted through the skin into the flexor carpi radialis, and temperature is read from a Leeds and Northrup Speedomax. If necessary, radiant heat is used to warm the muscle to approximately 35° C. The thermocouple is then withdrawn.

3] **Delimitation of motor point on skin.** This is performed in the usual way by stimulating percutaneously with a stigmatic electrode until low-threshold twitch response is elicited with shocks of 0.1 msec. duration. When subcutaneous fat is prominent and visual assessment of the response difficult, the tendon of the muscle can be palpated at the wrist.

4] **The functional state of the muscle** can be investigated before the surgical procedure. A pair of skin electrodes can be placed on muscle belly, at the motor point, and on tendon, and connected to the amplifier. The belly–tendon electrogram is recorded while trains of supramaximal shocks at various rates are delivered to the median nerve.[14]

5] **Surgical access to muscle.** The recording electrodes mentioned under 4 are taken away, and the skin overlying flexor carpi radialis is infiltrated with 2% Xylocaine. With full aseptic precautions, a longitudinal incision 4 to 5 cm. in length is made at the level of the previously determined motor point (Fig. 3A). The aponeurosis, brought to the view through dissection of subcutaneous tissue, is incised longitudinally and retracted in order to expose the upper surface of the muscle (Fig. 3B). One then sees parallel bundles of muscle fibers corresponding to the axis of flexor carpi radialis. These bundles originate from a limited portion of the upper part of the fascia and terminate on the superficial aspect of the distal tendon (see Figure 4, arrow). Their innervation band is running at a right angle to the direction of the muscle fibers, as required for accurate delimitation of end plates. Moreover, the innervation zone of this axial bundle corresponds fairly closely to the motor point

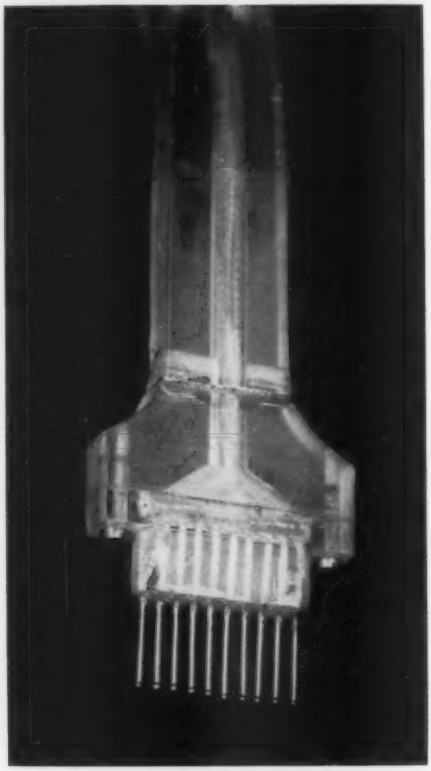

Fig. 5. Photograph of sterile recording system used; 10 platinum electrodes are separated by 2-mm. intervals and fixed in a Plexiglas holder which is long enough (26 cm.) to manipulate without touching the operating field. The 10 electrodes are connected with 10 cables which run through the center of the holder.

of flexor carpi radialis, as determined on the skin. Muscle bundles situated more medially and more laterally are not so suitable because these bundles are oriented obliquely and the innervation zone cannot so easily be sampled electrophysiologically.

6] **Oscillographic delimitation of end-plate region.** An array of 10 electrodes separated by 2 mm. intervals and embedded in a long Plexiglas holder is used (Fig. 5). The electrode assembly is sterilized for two days in a closed box containing trioxymethylene tablets. All connecting cables are included in the Plexiglas stump so that electrophysiologic manipulations occur at about 25 cm. from exposed muscle. Electrical connection is effected toward the amplifier input by a 10-way plug and selector. The Plexiglas holder is supported by a Palmer stand and lowered onto the operating field so that the row of electrodes is parallel to the investigated muscle bundle and makes a gentle contact with the muscle surface. Single shocks are then delivered to the median nerve while pairs of adjacent electrodes of the array are successively used for recording. The end plate focus is determined from the polarity of evoked muscle potentials.

7] **Excision of biopsy.** Fine cotton threads are sewn into the muscle bundle on either side of the delimited end plate zone, and the sample is excised with fine scissors. Two biopsy specimens can generally be investigated and taken from the axial part of the muscle. The specimens are processed with various methods such as vital methylene blue[6] and modified Koelle acetylthiocholine procedure.[6,13] Finally, the aponeurosis and skin are sutured.

RESULTS

The experimental data collected on the patients will be described in full elsewhere, but some results can be presented here to show the consistency and usefulness of the method as applied to man.

Figure 6 illustrates electrical responses recorded directly from the exposed surface of flexor carpi radialis when a single shock is applied to the median nerve. The 5 relevant electrodes of the recording array (Fig. 5) are represented by filled circles numbered from 1 to 5. The initial deflection of the evoked potential is downwards in A and B and upwards in C and D. With the convention adopted for connecting the leads to the amplifier, this means that the negative variation of the muscle spike propagates from either side of electrode 3 toward electrodes 1 and 5. In other words, electrode 3 appears to be closest to the end plate zone where the muscle impulse is initiated.

Consequently, with the electrode holder still on the muscle, fine threads are attached to the bundle at the level of electrodes 2 and 4 in order to be able to identify the position of

pickups later on. The electrode array is then removed, and the specimen excised and treated with the modified acetylthiocholine method, which stains selectively the cholinesterase of the subneural apparatus of the motor end plate. When the sections are examined under low power (Fig. 7), the end plates are seen as black dots neatly concentrated in a narrow band running across the fiber bundle. The holes left in the specimen by the threads have been blackened with ink and are easily recognized.

The positions occupied by electrodes 2, 3, and 4 during the sampling can thus be estimated reasonably accurately. Strikingly enough, the end plates are at about equal distance from the marks and coincide with the level of electrode 3 which had been identified as lying closest to the muscle spike focus in the electrical records of Figure 6. Such an agreement between electrophysiologic delimitation and subsequent histologic findings is now regularly obtained. Apparently, the method can reliably localize the end plate zone with an error of less than 2 mm.

However, such satisfactory results will only be obtained if the pictures seen on the oscilloscope are critically interpreted.[7] For instance, when the array of electrodes is not strictly parallel to the direction of the muscle bundle, the activity of different fiber fascicles will be recorded from the different leads. In this case, complex wave forms can be observed which

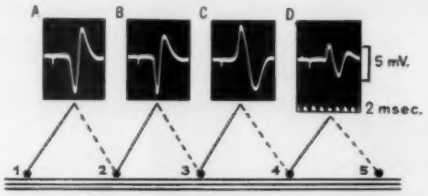

Fig. 6. Patient with mild myasthenia (No. 24 in Desmedt's series). Delimitation of end plate zone in flexor carpi radialis. Each tracing represents a cathode-ray oscillogram of the response evoked in the muscle by a single maximal shock on the median nerve. The polarity of the first deflection of the muscle spike clearly reverses on electrode 3.

are sometimes of opposite polarity. The electrode holder may be adequately oriented, but the end plates may become situated between a pair of adjacent leads rather than under one of the leads. The record obtained from two such electrodes will generally consist of a small complex potential change, and a clear-cut reversal will appear only when the next proximal and distal pairs of electrodes are compared. In our experience, it always pays to move the electrode holder until it stays in the optimal position in which large diphasic potentials are recorded from at least 4 adjacent pairs of leads (Fig. 6) and in which a clear-cut reversal from positive to negative polarity is seen in the potentials recorded from adjacent pairs having 1 common electrode.

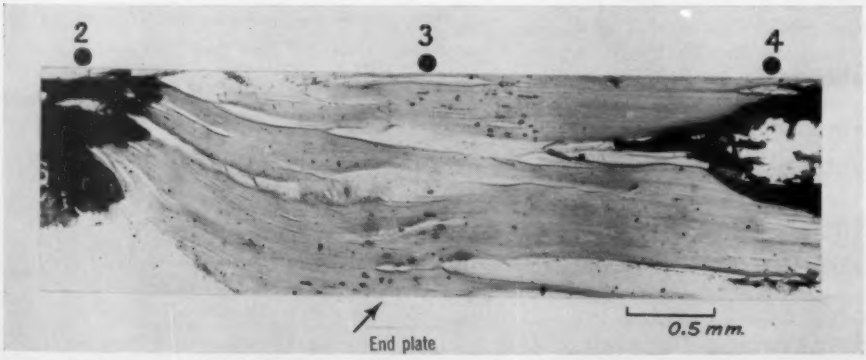

Fig. 7. Same patient as in Figure 6. Microphotograph of a longitudinal section through the excised biopsy specimen. The positions of electrodes 2, 3, and 4 at the time of the electrophysiologic sampling are indicated by filled circles. End plates are stained with the modified Koelle method.

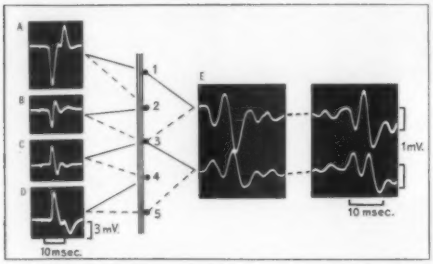

Fig. 8. Patient with moderately severe, generalized myasthenia (No. 18 in Desmedt's series). A to D = delimitation of end plate zone in flexor carpi radialis by recording muscle spike evoked by a single shock applied to the median nerve. There is a clear-cut reversal of the polarity of the potential on electrode 3. E = 2 samples from oscilloscope tracings obtained while the patient was instructed to flex the hand so as to voluntarily evoke motor unit discharges. The leads are connected as indicated, according to the usual convention. The potential reversal on electrode 3 also occurs for voluntary motor units.

We use evoked potentials in the electrophysiologic sampling of the muscle surface because it is much simpler to have the muscle fibers activated simultaneously. Yet, once the end plate focus has been delimited with the method described, it is possible to record voluntary motor unit potentials through the same electrodes (Fig. 8). Two oscilloscope channels are used simultaneously and are hooked up with critical electrode 3 as the common lead. The motor units illustrated on an expanded time-base also disclose a typical phase reversal under these conditions, which indicates that they are initiated at the same end plate focus.

SUMMARY

1] Electrophysiologic sampling of the exposed surface of a suitable muscle in man has been used to delimit the end plate region. The method is based on the observation of a reversal in the polarity of the muscle spike evoked by a single shock delivered to the motor nerve when the records obtained in a series of bipolar leads are compared. Such reversals occur at the focus of initiation of the muscle action potential which corresponds to the motor end plate.

2] The procedure used in the study of flexor carpi radialis muscle is detailed, and the consistency of the method is established by comparing electrophysiologic observations with the histologic findings on the same muscle sample after excision. (Compare Figs. 6 and 7.)

3] The method appears to be useful in 2 respects. First, it makes possible the excision of neuromuscular biopsies of minimal size including a limited amount of surrounding muscular tissue as required for electron microscopy. Second, comparison can be made of histopathologic and physiopathologic observations collected on the same muscle sample.

REFERENCES

1. Duchenne (de Boulogne), G. B.: De l'électrisation localisée et de son application à la pathologie et à la thérapeutique. Third edition, Bailliére, Paris, 1872.
2. Coërs, C.: Note sur une technique de prélèvement des biopsies neuro-musculaires. Acta neurol. et psychiat. belg. 53:759, 1953.
3. Desmedt, J. E.: Nature of the defect of neuromuscular transmission in myasthenic patients: post-tetanic exhaustion. Nature 179:156, 1957.
4. Pinelli, P., and Buchthal, F.: Muscle action potentials in myopathies with special regard to progressive muscular dystrophy. Neurology 3:347, 1953.
5. Jones, R. V., Jr., Lambert, E. H., and Sayre, G. P.: Source of a type of "insertion activity" in electromyography with evaluation of a histologic method of localization. Arch. Phys. Med. 36:301, 1955.
6. Coërs, C.: Les variations structurelles normales et pathologiques de la jonction neuromusculaire. Acta neurol. et psychiat. belg. 55:741, 1955.
7. Burns, B. D., and Paton, W. D. M.: Depolarization of the motor end-plate by decamethonium and acetylcholine. J. Physiol. 115:41, 1951.
8. Adrian, E. D., and Matthews, B. H. C.: The Berger rhythm: potential changes from the occipital lobes in man. Brain 57:355, 1934.
9. Walter, W. Grey: The electro-encephalogram in cases of cerebral tumour. Proc. Roy. Soc. Med. Lond. 30:579, 1937.
10. Brown, G. L., and Burns, B. D.: A convenient nerve-muscle preparation from the gracilis of the cat. J. Physiol. Lond. 108:54P, 1949.
11. Eccles, J. C., Katz, B., and Kuffler, S. W.: Nature of the "endplate potential" in curarized muscle. J. Neurophysiol. 4:362, 1941.
12. del Castillo, J., and Katz, B.: Biophysical aspects of neuromuscular transmission. Progr. Biophysics Lond. 6:121, 1956.
13. Couteaux, R., and Taxi, J.: Recherches histochimiques sur la distribution des activités cholinestérasiques au niveau de la synapse myoneurale. Arch. Anat. Microsc. Paris 41:352, 1952.
14. Desmedt, J. E.: Méthodes d'étude de la fonction neuromusculaire chez l'homme. Myogramme isométrique électromyogramme d'excitation et topographie de l'innervation terminale. Acta neurol. et psychiat. belg. 58:977, 1958.

Effects of diphenylhydantoin upon adrenal cortical function in man

Nicholas P. Christy, M.D., and Adele D. Hofmann, M.D.

AFTER OBSERVING mental disturbances and electroencephalographic changes in patients with Addison's disease[1] and Cushing's syndrome,[2] and, after occasionally observing psychoses and convulsive seizures in patients receiving cortisone and ACTH,[3] many investigators examined the relationship between the adrenal cortex and cerebral excitability.

The problem has been reviewed by Glaser.[4] Cortisone lowers and desoxycorticosterone raises the electroshock-seizure threshold in animals and human beings.[4,5] Because of the influence of endogenous and exogenous steroids on the convulsive state, the possible effects of anticonvulsant drugs upon adrenal cortical function were studied.

Emmett and associates,[6] Staple,[7] and Woodbury[5] investigated the effects of chronic administration of diphenylhydantoin sodium to guinea pigs, mice, and rats. Using amounts of the drug proportionately 2 to 20 times as great as usual therapeutic doses given to human subjects, these workers were able to show appreciable increases in adrenal weight in twenty to one hundred twenty-five days. The functional significance of the observed adrenal hypertrophy seemed questionable after Staple's later finding of degenerative lesions in the adrenal cortex of mice after long-time administration of diphenylhydantoin.[8] Functional significance was also questioned after Bonnycastle and Bradley's observation that acute or chronic administration of diphenylhydantoin inhibited the adrenal cortical response to many stressful stimuli.[9]

In man, evidence of a possible effect of diphenylhydantoin on the adrenal cortex has come from 3 directions. *First*, the rare instances of hirsutism associated with diphenylhydantoin treatment have raised the question of adrenal cortical involvement, although no evidence at present supports this idea.[10] *Second*, Bray, Ely, and Kelley[11] showed diminished responses of plasma 17-OH-corticosteroid levels to intramuscular corticotrophin in 19 children with unspecified convulsive disorders who had received diphenylhydantoin for two months or more. This finding could not be explained by a more rapid rate of disappearance of 17-OH-corticosteroid from plasma.[12] *Third*, Costa, Glaser, and Bonnycastle[13] reported a decrease in the excretion of urinary 17-ketosteroids and corticosteroids during diphenylhydantoin treatment of 12 adult patients for twenty-one to sixty days.

These 2 groups of investigators suggested that an ancillary effect of diphenylhydantoin upon cerebral excitability might be mediated through a degree of adrenal cortical suppression.[11,13]

The present study reevaluates the effect upon adrenal cortical function of long-term diphenylhydantoin administration in man. The results suggest that children are affected differently by the drug than are adults. In the adult group, the data indicate that no reduction occurs in adrenal cortical activity as measured by plasma steroid response to ACTH.

MATERIALS AND METHODS

Patients with convulsive disorders. The adult group consisted of 6 males and 5 females from 16 to 74 years old. Of these, 7 had seizures of unknown etiology and 4 had vascular, neoplastic, or demyelinating disease. In none was there evidence of widespread brain damage—specifically, of hypothalamic dysfunction—

From the departments of Medicine and Pediatrics, the College of Physicians and Surgeons, Columbia University, New York City.

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Dr. Christy is a John and Mary R. Markle Scholar in Medical Science.

Dr. Hofmann's present address is Department of Pediatrics, St. Luke's Hospital, New York City.

TABLE 1

PLASMA 17-OH-CORTICOSTEROID RESPONSE TO INTRAVENOUS CORTICOTROPHIN IN ADULTS TREATED WITH DIPHENYLHYDANTOIN

Patient	*Age*	*Sex*	*Diagnosis*	*Dose of diphenyl-hydantoin, grams per day*	*Months' duration of treatment*	*Plasma 17-OH-CS, μg. per cent* *Before ACTH*	*After ACTH*	*Increment*
JM	23	M	Seizures of unknown etiology	0.3–0.4	96	35	57	22
HS	26	F	"	0.4–0.6	168	5	40	35
AG	33	M	"	0.2–0.3	54	4	47	43
PW	44	F	"	0.3	36	15	42	27
VM	51	M	"	0.3	24	15	31	16
GB	56	M	"	0.2–0.4	108	43	67	24
WW	74	M	"	0.3	18	23	47	24
LT	16	F	Glioblastoma multiforme	0.4	28	24	59	35
FR	34	F	Disseminated sclerosis	0.4	20	27	52	25
VS	42	F	Intracerebral hematoma	0.5	18	17	36	19
HH	52	M	Thrombosis, right internal carotid	0.3–0.5	11	18	35	17
Average	41			0.28–0.40	53	21	47	26*

*Increment not significantly different from that in 40 normal subjects; plasma 17-OH-CS before ACTH, 17 μg. per cent; after ACTH, 46; increment, 29[19]

which might interfere with the operation of the pituitary-adrenal system.[14]

The children's group consisted of 4 males and 3 females 8 to 21 years old at the time of observation. Each had seizures of unknown etiology, and treatment with diphenylhydantoin was started in each well before the onset of puberty. None of the subjects in either group were acutely ill at the time of study.

Assessment of adrenal cortical function. The response of plasma 17-OH-corticosteroid levels to a four-hour intravenous infusion of 25 units of corticotrophin was the measure of adrenal cortical function. The method has been reported in detail elsewhere.[15–17] By a similar testing procedure, untreated patients with seizures have shown normal responses.[11]

To rule out possible effects of diphneylhydantoin upon the colorimetric methods used in steroid determinations of blood and urine, diphenylhydantoin was tested in the Silber-Porter[15] and Holtorff-Koch[18] procedures for plasma 17-OH-corticosteroids (hydrocortisone) and urinary 17-ketosteroids, respectively.

RESULTS

Table 1 shows the results of four-hour intravenous corticotrophin tests performed in 11 adult patients administered diphenylhydantoin alone for eleven to one hundred sixty-eight months. The average plasma 17-OH-corticosteroid response of this group did not differ appreciably from that observed in a group of 40 subjects without adrenal cortical disease;[19] 8 patients had responses within normal limits, 2 had elevated plasma steroid levels both before and after ACTH, and 1 had slightly subnormal response.

Table 2 summarizes the data obtained from the 7 patients in whom diphenylhydantoin treatment was started in childhood. The subjects had received the drug for thirteen to ninety-six months. Average response of plasma steroid to intravenous corticotrophin was subnormal and significantly less than that observed in the diphenylhydantoin-treated adults ($P < 0.01$).

Of the patients, 2 had normal ACTH responses. The rest had subnormal steroid rises after ACTH. The average pre-ACTH plasma 17-OH-corticosteroid level in the children of 18 μg. per cent did not differ appreciably from the average adult control value of 21 μg. per cent.

Three groups of data appeared to weigh against an enhancing or inhibitory effect of diphenylhydantoin upon the colorimetric methods used for steroid determination.

1] Chromatography[20] of the ethyl acetate extract of a plasma pool obtained after ACTH tests from 3 of the diphenylhydantoin-treated adults revealed a hydrocortisone spot. The spot was estimated by ultraviolet light absorption to contain 53 μg. per cent of the steroid, compared to 57 μg. per cent according to the Silber-Porter technic;[15] 93.4% of the Porter-Silber chromogen could be quantitated as hydrocortisone.

2] Addition of diphenylhydantoin in quantities thought to be present in plasma of chronically-treated patients—1 to 50 μg. per cubic centimeter[21,22]—to known amounts of hydrocortisone caused no reduction in the chromogenicity of the steroid as determined by Porter-Silber reaction.[15]

3] To test the drug's reportedly inhibitory effect on urinary 17-ketosteroid excretion,[13] 20 mg. of diphenylhydantoin was added before acid hydrolysis to the 100 cc. aliquots of 10 twenty-four-hour urine specimens on which the Holtorff-Koch method[18] for urinary 17-ketosteroids was performed. Diphenylhydantoin in this quantity produced no diminution in Zimmerman chromogen which could be considered significant. Average control value for 17-ketosteroids of the 10 specimens was 10.2 mg. per twenty-four hours and with added diphenylhydantoin, 9 mg. per twenty-four hours ($P > 0.04$).

DISCUSSION

Finding a reduced adrenal cortical response to ACTH which is apparently not artifact in a small group of children treated with diphenylhydantoin confirms the observation of Bray and associates.[11] Apparently, diphenylhydantoin did not seriously interfere with the colorimetric reaction for plasma 17-OH-corticosteroids, since in this study and that of Bray and associates,[11] the pre-ACTH steroid levels were essentially the same in diphenylhydantoin-treated children and adults and in untreated subjects (Table 1). This possibility had to be definitely excluded, however, because certain drugs, for instance, chlorpromazine, are capable of interfering in the color reaction, causing falsely low values.[17] Although, in the report of Bray, Ely, and Kelley,[11] steroid response to ACTH was subnormal following diphenylhydantoin, the fall in circulating eosinophils after corticotrophin was normal.

The failure to show reduced adrenal cortical response in diphenylhydantoin-treated adults is difficult to explain in view of the earlier reports.[11,13] The present study appears to suggest a difference between children and adults in adrenal cortical susceptibility to suppression by diphenylhydantoin.

The apparent difference could conceivably be explained by at least 3 factors:

1] A fundamental and obscure difference may exist between the prepuberal and the

TABLE 2

PLASMA 17-OH-CORTICOSTEROID RESPONSE TO INTRAVENOUS CORTICOTROPHIN IN PATIENTS IN WHOM TREATMENT WITH DIPHENYLHYDANTOIN WAS STARTED BEFORE PUBERTY

Patient	*Age*	*Sex*	*Diagnosis*	*Dose of diphenylhydantoin, gram per day*	*Months' duration of treatment*	*Plasma 17-OH-CS, μg. per cent Before ACTH*	*After ACTH*	*Increment*
MA	8	F	Seizures of unknown etiology	0.1–0.2	26	26	24	–2
AT	10	M	"	0.1–0.2	96	18	30	12
HHa	11	M	"	0.2–0.3	64	21	30	9
VK	12	F	"	0.2	19	14	36	22
GW	14	M	"	0.3–0.6	13	8	20	12
BH	16	F	"	0.5	36	20	34	14
FH	21	M	"	0.4–0.5	96	19	23	4
Average	13			0.22–0.36	80	18	28	10*

*Average increment is significantly less than the average increment of 26 observed in diphenylhydantoin-treated adults (Table 1) and less than the average increment in normal children.[11]

$$\text{S.E.D.} = \sqrt{s^2 \frac{n_1 + n_2}{n_1 n_2}} = 5.2,\ t = 3.08,\ P < 0.01.$$

adult pituitary-adrenal system which makes children more sensitive to this chemical influence.

2] A higher ratio of drug dose to body weight may occur in children.

3] The eighty months' duration of diphenylhydantoin treatment in children and the only fifty-three months' treatment in the adults does not appear to be crucial. Of the children, 1 had a normal steroid response after thirty-six months of diphenylhydantoin, while another had diminished reaction after a year's treatment (Table 2).

The consistently normal ACTH responses of the adult group do not agree with the reduction in steroid excretion in a group of adult patients reported by Costa and associates.[13] Differences in duration of diphenylhydantoin administration and in the method of assessing adrenal cortical function may explain the discrepancy, but neither of these 2 factors satisfactorily accounts for the discordant findings.

No convincing explanation is apparent for the difference in adrenal cortical response between children and adults treated with diphenylhydantoin or for the discrepancy between lack of diphenylhydantoin effect on the adult adrenal cortex found in the present study and the suppressive effect reported by Costa and associates.[13] But, apparently, the beneficial effects of diphenylhydantoin on the convulsive state in adults cannot be partially attributed to a degree of adrenal cortical suppression.[11,13]

SUMMARY

In 11 adults with convulsive disorders, plasma corticosteroid responses to intravenous corticotrophin were in normal range following prolonged administration of diphenylhydantoin. In 7 patients with convulsive disorders in whom diphenylhydantoin treatment was started before puberty, the average plasma corticosteroid response to ACTH was subnormal. The difference is not explained, but, in adults at least, it appears unlikely that a reduction in adrenal cortical responsiveness plays an important role in mediating the beneficial effects of diphenylhydantoin upon seizure threshold.

The authors are grateful to the departments of Neurology, Columbia University College of Physicians and Surgeons, for making patients available for study.

REFERENCES

1. Engel, G. L., and Margolin, S. G.: Neuropsychiatric disturbances in internal disease. Arch. Int. Med. 70: 236, 1942.
2. Glaser, G. H.: Psychotic reactions induced by corticotropin (ACTH) and cortisone. Psychosom. Med. 15:280, 1953.
3. Baehr, G., and Soffer, L. J.: Treatment of disseminated lupus erythematosus with cortisone and adrenocorticotropin. Bull. New York Acad. Med. 26:229, 1950.
4. Glaser, G. H.: On relationship between adrenal cortical activity and convulsive state. Epilepsia 2:7, 1953.
5. Woodbury, D. M.: Effects of chronic administration of anticonvulsant drugs, alone and in combination with desoxycorticosterone, on electroshock seizure threshold and tissue electrolytes. J. Pharmacol. & Exper. Therap. 105:46, 1952.
6. Emmett, A. D., Hartzler, E. R., and Brown, R. A.: Effect of sodium diphenyl hydantoinate (dilantin sodium) on utilization of ascorbic acid by guinea pigs. J. Pharmacol. and Exper. Therap. 78:215, 1943.
7. Staple, P. H.: Action of diphenylhydantoin sodium on the adrenal gland. Lancet 1:1074, 1951.
8. Staple, P. H.: Diphenylhydantoin, adrenal function and epilepsy. J. Endocrinol. 9:xviii, 1953.
9. Bonnycastle, D. D., and Bradley, A. J.: Blocking action of dilantin upon the pituitary-adrenal system. Fed. Proc. 15:403, 1956.
10. Goodman, L. S., and Gilman, A.: Pharmacological Basis of Therapeutics, New York City, Macmillan, 1955, p. 186.
11. Bray, P. F., Ely, R. S., and Kelley, V. C.: Studies of 17-hydroxy-corticosteroids; adrenocortical function in patients with convulsive disorder. Arch. Neurol. & Psychiat. 72:583, 1954.
12. Bray, P. F., Zapata, G., Ely, R. S., and Kelley, V. C.: Influence of adrenal function on treatment of epilepsy. Proc. Meet. American Acad. Neurol., 1958.
13. Costa, P. J., Glaser, G. H., and Bonnycastle, D. D.: Effects of diphenylhydantoin (dilantin) on adrenal cortical function. Arch. Neurol. & Psychiat. 74: 88, 1955.
14. Harris, G. W.: Neural Control of the Pituitary Gland, London, Edward Arnold, 1955.
15. Silber, R. H., and Porter, C. C.: Determination of 17,21-dihydroxy-20-ketosteroids in urine and plasma. J. Biol. Chem. 210:923, 1954.
16. Christy, N. P., Wallace, E. Z., and Jailer, J. W.: Effect of intravenously-administered ACTH on plasma 17,21-dihydroxy-20-ketosteroids in normal individuals and in patients with disorders of adrenal cortex. J. Clin. Invest. 34:899, 1955.
17. Christy, N. P., Longson, D., Horwitz, W. A., and Knight, M. M.: Inhibitory effect of chlorpromazine upon adrenal cortical response to insulin hypoglycemia in man. J. Clin. Invest. 36:543, 1957.
18. Holtorff, A. F., and Koch, F. C.: Colorimetric estimation of 17-ketosteroids and their application to urine extracts. J. Biol. Chem. 135:377, 1940.
19. Christy, N. P., Wallace, E. Z., and Jailer, J. W.: Comparative effects of prednisone and of cortisone in suppressing response of adrenal cortex to exogenous adrenocorticotropin. J. Clin. Endocrinol. 16:1059, 1956.
20. Burton, R. B., Zaffaroni, A., and Keutmann, E. H.: Paper chromatography of steroids; corticosteroids and related compounds. J. Biol. Chem. 188:763, 1951.
21. Dill, W. A., Kazenko, A., Wolf, L. M., and Glazko, A. J.: Studies on 5,5'-diphenyl-hydantoin (dilantin) in animals and man. J. Pharmacol. & Exper. Therap. 118:270, 1956.
22. Plaa, G. L., and Hine, C. H.: Method for simultaneous determination of phenobarbital and diphenylhydantoin in blood. J. Lab. & Clin. Med. 47:649, 1956.

Hallucinatory effect in man of acetylcholine inhibitors

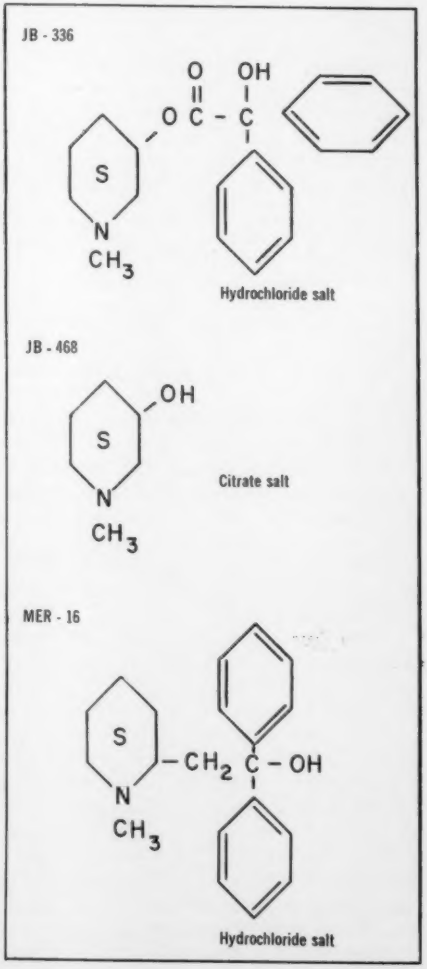
Carl C. Pfeiffer, M.D., Henry B. Murphree, Elizabeth H. Jenney, Mason G. Robertson, M.D., A. Henry Randall, M.D., and Laurance Bryan

IN MAN, many of the symptoms of the hallucinogen LSD-25 are not unlike those of atropine. These symptoms are facial flush, rise in blood pressure, dilation of the pupils, and rise in body temperature. The hallucinatory effect of atropine in overdosage is well known—a toxic delirium occurs with doses between 5 and 8 mg.

In animals, we have shown that muscarinic stimulation of the brain produces parkinsonian tremor and that the control of this tremor with atropine or scopolamine is a time honored procedure.[1]

In this experiment, we have used a drug-sophisticated group of healthy volunteers at the Atlanta Penitentiary. These men can differentiate accurately between 0, 25, 50, and 100 μg. of LSD.[2] Tests of atropine derivatives were done under double-blind test conditions except that commercial tablets were used. However, the tests were done in groups of 4 trials, and the subjects did not know the nature of the tablets.

Abood[3] finds that oral administration of 10 to 20 mg. of JB-318, the tertiary amine analogue of Piptal, or JB-336, the n-methyl derivative of JB-318, produces a model psychosis characterized by visual and auditory hallucinations. We have not been able to give doses larger than 9 mg. because of the extreme mental effects.



From the Department of Pharmacology, Emory University, Atlanta.

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DOUBLE BLIND STUDY OF EXPERIMENTAL HALLUCINOGENS AND ANTITREMOR DRUGS FOR THEIR LSD-25-LIKE EFFECT IN NORMAL HUMAN SUBJECTS

	Drug	Dose (mg.)	Results
Experimental Hallucinogens	JB-336	6	6/6† = 75 LSD
	JB-336	9	3/3 = 100–150 LSD
	JB-468	100	0/6 = Sedative effect only
	MER-16	150	8/8 = 150+ LSD*
Antitremor drugs	Artane	5	6/8 = 25–50 LSD
	Artane	10	5/5 = 100–150 LSD**
	Pagitane	5	6/8 = 25–50 LSD
	Panparnit	25	4/8 = 25–50 LSD
	Cogentin	2	3/8 = 25–50 LSD
	Kemadrin	15	3/8 = 25 LSD
	Parsidol	50	3/8 = 25 LSD
	Disipal	100	2/8 = 25 LSD
	Benadryl	100	2/8 = 25 LSD
	Atropine	2	1/8 = 25 LSD
	Scopolamine	2	1/8 = 25 LSD

† 6 out of 6 subjects likened this to 25 to 50 μg. LSD-25.
* Effect lasts three days.
** Bradycardia in all subjects; extrasystoles in 2

A similar possible acetylcholine antagonist, MER-16, produces extreme LSD-like effects when 150 mg. is given orally. Hallucinations last for three days and are characterized by repeated waves of depersonalization, visual hallucinations, and feelings of unreality. Because of these interesting findings with acetylcholine antagonists, we studied most of the compounds which are now used to treat parkinsonism (see table). Without exception, when adequately large dosage is used, these atropine congeners produce an effect which the subjects liken to LSD-25.

These drugs are more effective than either scopolamine or atropine in producing hallucinatory effects. Scopolamine was no more active as an hallucinogen than atropine, but 2 mg. of scopolamine produced a sedative and sleep-producing effect lasting three days. The simple alcohol of JB-336, called compound JB-468, did not produce hallucinations in the dosage used—100 mg. of the citrate salt given orally. The subjects did report a sedative action of JB-468, and this compound may be analogous in its pharmacologic action to Laborit's compound SCTZ, which is reported to have a sleep-producing effect.

CONCLUSIONS

1] Synthetic atropines, both marketed and unmarketed, are more active hallucinogens than either atropine or scopolamine.

2] Some of these produce hallucinatory effects lasting twenty-four to forty-eight hours.

3] The recommended daily dosage of many of these antitremor drugs produces hallucinations in single trials in healthy subjects.

4] The parkinsonian patient may possibly be more resistant to the hallucinatory effect than is the healthy subject, and the recommended dosage schedules would tend to produce tolerance to the hallucinatory effect.

5] The newer synthetic antitremor drugs have fewer peripheral side actions, but the central side actions, such as hallucinations, are exaggerated and should be anticipated.

REFERENCES

1. Pfeiffer, C. C., and Jenney, E. H.: The inhibition of the conditioned response and the counteraction of schizophrenia by muscarinic stimulation of the brain. Ann. New York Acad. Sc. 66:753, 1957.
2. DeMaar, E. W. J., Williams, H. L., Miller, A. L., and Pfeiffer, C. C.: Effects in man of single and combined oral doses of reserpine, iproniazid and d-lysergic acid diethylamide. Unpublished.
3. Abood, L. G.: New class of psychotogenic agents. Presented at Brain Research Foundation Scientific Conference, New York City, Jan. 25, 1958.

Acute effects of x-radiation on reflex arcs of the spinal cord

K. Carrington, M.D., F. D. Fowler, M.D., and
E. A. Bering, Jr., M.D.

THE SPINAL CORD provides a localized segment of the nervous system where both conduction and neuronal interaction occur and any change of either type of activity can easily be detected. This paper presents a study of the acute effects of x-radiation on the reflex arcs of the spinal cord as measured by electrophysiologic methods.

The effects of total body irradiation and local irradiation of the central nervous system, particularly in the brain, have been investigated, but the spinal cord has received little specific attention. Most of the experimental work done on the spinal cord before 1954[1] was chiefly concerned with determining the amount of radiation required to produce paraplegia and the associated histologic changes. However, McLaurin and associates did some preliminary studies on the electrical activity of the spinal cord.[9]

Gerstner[3] and Konecci[5] have recently studied sensory preception and motor response after irradiation of the spinal cord. They found that during the first two to three hours after irradiation, some animals appeared to be hypersensitive and reaction time between sensory stimulation and motor activity was decreased. This decrease was followed by an increase in reaction time with total abolition of the response if high enough doses of radiation were given.

Knowledge of the effects of radiation on the human spinal cord is limited to the occurrence of paraplegia after irradiation of malignant tumors. Although radiation doses which cause paraplegia are not consistent,[2,8-12,14] about 3,000 r seems to be the critical dose. Paraplegia is reported to have occurred from one to fifteen months after irradiation.

MATERIALS AND METHODS

In these experiments, 25 cats were studied; 15 were controls, and 10 were irradiated. Radiation was given by a Phillips deep x-ray therapy unit at 250 kv. 15 ma. without filtration at a tube to target distance of 40 cm. The rate of delivery was 250 r per minute. Eletroencephalographic recordings were made with a Grass III D 8 channel electroencephalograph. A Grass S4B stimulator with isolation unit was used for stimulation. Spinal cord recordings were made with a preamplifier and a DuMont 333 dual beam oscilloscope photographed with a Grass C4C kymograph camera.

To study the possible effects of pentobarbital anesthesia, 10 cats were given pentobarbital intravenously in measured amounts and the effect noted on the electroencephalogram. In 4 of these cats, the spinal cord was exposed and recordings were made from the L7 anterior root with the L7 posterior root being stimulated. Vinethene and ether were administered to 12 cats. Bilateral carotid ligation and tracheotomy were performed and the animals' spinal cords completely transected under direct vision at the level of C1. Respiration was maintained by a positive pressure respirator. The cats were allowed to recover completely from the Vinethene and ether anesthesia.

A total laminectomy was then performed from L1 to L7, and the anterior and posterior roots of L7 on either side were isolated and cut and crushed at their junction with the dura. Bilateral stimulating electrodes with approximately 4 mm. between the electrodes were

From the Neurosurgical Research Laboratory of the Children's Medical Center, Boston. This investigation was supported by U.S.P.H.S. Grant C-1608(C4) from the National Institutes of Health.

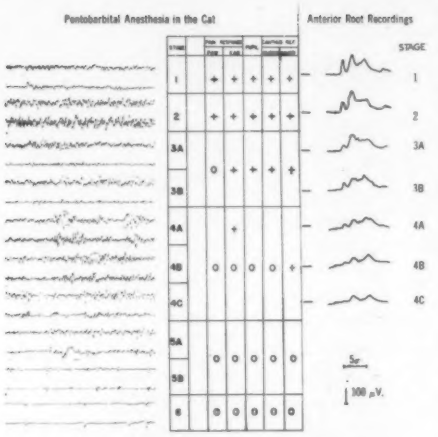

Fig. 1. The effect of pentobarbital anesthesia on the cat as measured by electroencephalogram, clinical tests, and the spinal cord reflex. The spinal cord reflex activity was recorded on L7 anterior root after stimulating L7 dorsal root.

placed on the posterior root, and bilateral recording electrodes were placed on the anterior roots. The spinal cord, roots, and electrodes were covered with mineral oil to prevent drying, and the animals were kept warm with heat lights and hot water bottles. Of this group, 5 were used as controls.

Recordings were taken from the anterior root with posterior root stimulation every twenty minutes for periods up to twelve hours. The same procedure was done in the remaining 7 cats, but after control recordings had been obtained for approximately twenty minutes, each of these cats was removed from the apparatus and given 5,100 r at the rate and under the specifications given. This radiation was delivered over the area L1 to L7 to the exposed spinal cord. The cats were then returned to the apparatus and anterior root recording made with posterior root stimulation approximately every twenty minutes up to eleven hours after irradiation. All the animals were sacrificed, and the spinal cords were removed for histologic study.

To demonstrate the clinical effect of the irradiation, 3 cats were used as controls. They were anesthetized with Nembutal and 5,100 r measured in air given to their spinal cords through one port at the level L1 to L7. These cats were allowed to recover and were observed until they died or were sacrificed.

RESULTS

Changes were seen in both the electroencephalographic and spinal cord reflexes in relation to the depth of anesthesia. As measured by the electroencephalograph, the cats passed through 6 rather distinct levels of anesthesia between wakefulness and death. Sequence reversed on awakening from the anesthetic, but the levels were not as distinct. The cats were difficult to maintain at a specific level of anesthesia, and, once the aninal had started to awaken, a specific level was difficult to reproduce with a predetermined amount of drug.

The anterior root response to a constant posterior root stimulus also changed progressively with increasing depth of anesthesia but did not show definite patterns as did the electroencephalogram. The amplitude of the response progressivaly declined, and the polysynaptic complex persisted after the monosynaptic spike was no longer apparent. This effect on local activity in the spinal cord, as well as on cerebral activity, suggests a widespread effect of pentobarbital in the central nervous system. These results are illustrated in Figure 1.

Because of the effect of pentobarbital on the anterior root response and the difficulty of maintaining a cat in a definite, reproducible level of anesthesia, no accurate analysis of radiation effects could be made if pentobarbital was used; therefore, the experiments were performed in spinal cats where anesthesia created no problem.

The 3 cats used as radiation controls received 5,100 r through the intact vertebral column and recovered from the intraperitoneal Nembutal anesthesia in approximately twelve hours. For the first twenty-four to thirty-six hours, the hind legs of these cats were apparently weak; the animals staggered when they walked, but their reflexes were within normal limits.

On the second day after irradiation, the cats ran about without difficulty or signs of myelitis. However, on the sixth or seventh day after irradiation, the animals again showed

signs of weakness in their hind legs and, within forty-eight hours, complete paraplegia was present. The animals died or were sacrificed soon after. Autopsy and histologic examination were performed but will not be discussed here.

In suitably prepared spinal cats, both monosynaptic and polysynaptic reflexes were recorded from the 5 control animals and from 7 animals before and after irradiation. Recordings on the control animals were taken approximately twenty minutes apart up to nine hours after the first recording; 3 stimuli were used—approximately threshold and 2 and 3 times threshold. Strength duration curves were done in 3 of the control animals and found to be essentially constant over a six-hour period. The wave form of the anterior root recordings remained constant and had the general characteristics of the monosynaptic and polysynaptic responses which have been described by others.[7]

The records were analyzed for time interval from stimulus to the first response (referred to as the response time), total duration of the response, and amplitude of the responses in each millisecond period after the stimulation. In 119 records from the control animals, the mean time from stimulation to the first response was $1.97 \pm .063$ msec. Analysis of the total duration of the response gave a mean of 10.07 ± 4.08 msec. Throughout the observation period of nine to eleven hours, these values remained constant within statistical limits.

Since the amplitude of the responses varied depending on the strength and character of the stimulus, no analysis was made.

The records taken from the 7 irradiated animals were analyzed at intervals of one-half hour, one hour, and then every hour for eleven hours after irradiation. The recordings from each period were subjected to analysis and compared with the control group. In the first period (0 to one-half hour) after irradiation, the response is not unlike the control recordings, although greater amplitude of response is suggested, especially in the late polysynaptic complex. The time from stimulation to response is not statistically prolonged nor is the total length of the response. In the second period (one-half to one hour), monosynaptic response is greatly increased in amplitude, compared to the control, with approximately the same relative stimulus being used. Again, no statistical increase occurs in reaction time or in the total length of the response. Between the first and second hour after irradia-

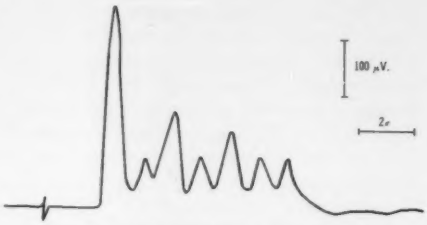

Fig. 2. Control recording of spinal cord reflexes taken from L7 anterior root after stimulation of L7 dorsal root. The first large spike is the monosynaptic response followed by the polysynaptic complex.

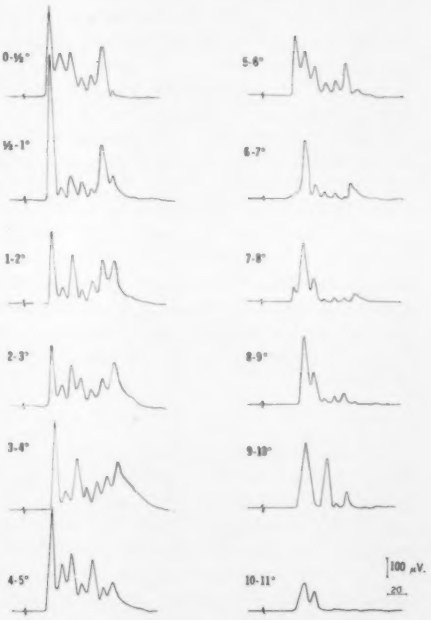

Fig. 3. The acute effect of irradiation on the reflex arcs of the spinal cord. Recordings made from L7 anterior root after L7 dorsal root stimulation. The times refer to hours after irradiation.

tion, amplitude decreases slightly and the response remains fairly stable for the next two hours, although increase in the response time is suggested. By six hours after irradiation, response time was definitely increased to a mean time of 2.77 msec., which was significant at the 3.5% level. The monosynaptic response was present, and the over-all duration of the response was unchanged.

The time between stimulus and response continued to lengthen throughout the eleven-hour observation period. As this lengthening of the response time continued, amplitude of the responses declined particularly in the polysynaptic response, but little change occurred in the total duration of the response until about eleven hours after irradiation. Then the polysynaptic response had almost completely disappeared. The monosynaptic response was always present, and, although amplitude was extremely reduced, the response remained a simple spike. These changes are shown in Figure 3.

The threshold for stimulation increased after irradiation, but the data were insufficient for detailed statistical analysis. In general, however, the threshold increased 2 or 3 times during the first hour following irradiation and then fell to a fairly constant value that was 30 to 50% higher than the threshold before irradiation.

DISCUSSION

The changes in the spinal cord reflex seen after irradiation are certainly different from those following pentobarbital anesthesia and, apparently, are different from the effects of anoxia.[13] The changes represent a real deviation from the control studies, and we may assume that these changes are the direct result of irradiation.

The biologic effects of irradiation depend on both total dose and rate of delivery.[14] The dose of 5,100 r delivered in these experiments is definitely above the threshold for the production of paraplegia, but, as the latent period is several days, the effects recorded in these experiments were probably not associated with permanent paraplegia but with transient weakness noticed during the same period after irradiation. If this is true, the recorded reflex changes are probably reversible, since the cats regained their strength and function. However, no studies were made during the recovery period, and more data are needed to confirm this point.

The increasing response time probably represents a decrease in conduction rate. Slowing of conduction rates does occur in peripheral nerves four or five hours after irradiation,[4] just as recorded here. The present work suggests that such slowing of conduction also occurs in the central nervous system. Whether the decrease in conduction rate is limited to the afferent limb alone or is general cannot be determined from these data. The consistency of the over-all duration of the response suggests that this decrease is at first general and is not specific for special types of fibers.

The effects seen on the polysynaptic response suggest change in the interneuronal activity of the spinal cord as well as decrease in the conduction rates.

This change could be caused by alterations in the subliminal pool which are secondary to a decreased input stimulus resulting from conduction changes. However, the disproportion between the changes of the monosynaptic and the polysynaptic responses is against this. Probably, this change is either of the neuronal bodies or the terminals of the neurons. Lee[6] suggested that such terminal alteration is one of the effects of radiation.

SUMMARY

1] In cats, 5,000 r of 250-kv. x-ray were given to the exposed lumbar spinal cords. Some of the animals were observed for clinical effect, and some were studied for electrophysiologic changes in spinal cord reflexes.

2] Some early weakness was observed but completely disappeared in twenty-four hours. Complete paraplegia developed on the sixth or seventh day.

3] Anterior root responses to posterior root stimulation before and immediately after irradiation were investigated. By the fifth hour after irradiation, response time became significantly delayed. This delay meant conduction rates were slower. The total length of time of the response was not significantly changed until nine to ten hours after irradiation. The polysynaptic response gradually diminished in amplitude, and, eleven hours after irradiation,

was almost absent. At this time, the monosynaptic spike showed marked reduction in amplitude but was never more than a single spike. This later suggested cellular or synaptic alterations.

4] The effect of pentobarbital on the cat electroencephalogram was investigated; 6 fairly distinct electroencephalographic patterns were found associated with increasing depth of anesthesia. As the cat goes into lower levels of anesthesia, the anterior root response with posterior root stimulation is significantly altered; pentobarbital should not be used when this response is being studied.

REFERENCES

1. Bering, E. A., Jr., Bailey, O. T., Fowler, F. D., Dillard, P. H., and Ingraham, F. D.: Effect of gamma radiation on central nervous system. Am. J. Roentgenol. 74:686, 1955.
2. Boden, G.: Radiation myelitis of cervical spinal cord. Brit. J. Radiol. 21:464, 1948.
3. Gerstner, H. B., Konecci, E. B., and Taylor, W. B.: Effect of local brain x-irradiation on pinna reflex of guinea pigs. Radiation Res. 1:262, 1954.
4. Gerstner, H. B., Orth, J. S., and Richey, E. O.: Effect of high-intensity x-radiation on velocity of nerve conduction. Am. J. Physiol. 180:232, 1955.
5. Konecci, E., and Danford, M. B.: Spinal reflex activity and local x-irradiation. U. S. Air Force School of Aviation Med., Randolph Field, Tex., Report 56-90, 1956.
6. Lee, J. C., Helgason, S., and Snider, R. S.: Effects of acute x-irradiation on evoked cerebellar response. Radiation Res. 3:267, 1955.
7. Lloyd, D. P. C.: Reflex action in relation to pattern and peripheral source of afferent stimulation. J. Neurophysiol. 6:111, 1943.
8. Malamud, N., Boldrey, E. B., Welch, W. K., and Fadell, E. J.: Necrosis of brain and spinal cord following x-ray therapy. J. Neurosurg. 11:353, 1954.
9. McLaurin, R. L., Bailey, O. T., Harsh, G. R., III, and Ingraham, F. D.: Effects of gamma and roentgen radiation on intact spinal cord of monkey. Am. J. Roentgenol. 73:827, 1955.
10. Paterson, E., and Farr, R. F.: Cerebellar medulloblastoma: Treatment by irradiation of whole central nervous system. Acta radiol. 39:323, 1953.
11. Smithers, D. W., Clarkson, J. R., and Strong, J. A.: Roentgen treatment of cancer of esophagus. Am. J. Roentgenol. 49:606, 1943.
12. Stevenson, L. D., and Eckhardt, R. E.: Myelomalacia of cervical portion of spinal cord, probably result of roentgen therapy. Arch. Path. 39:109, 1945.
13. Tarlov, M.: Spinal Cord Compression. Springfield, Ill., Charles C Thomas, 1957.
14. Itabashi, H. H., Bebin, J., and DeJong, R. N.: Post-irradiation cervical myelopathy. Neurology 7:844, 1957.

Disseminated sclerosis

A survey of patients in the Kingston, Ontario, area

D. Naldrett White, M.D., and Lorna Wheelan, M.B.

FROM THE NUMEROUS and sometimes conflicting studies and hypotheses concerning the etiology of disseminated sclerosis in recent years, a series of studies has emerged tending to relate this disease to those conditions, particularly studied in cattle, in which demyelinization occurs in the central nervous system as a result of a deficiency or excess of trace elements. The first of these studies was carried out by Bennetts and Chapman[1] in West Australia. They investigated swayback disease in lambs, a disease that produces, except in the mild cases, progressive symptoms of ataxia and spastic paralysis. Histologically, swayback disease is characterized by a symmetrical cerebral demyelinization followed by extensive cavitation and liquefaction in severe cases. The disease somewhat resembles Schilder's disease in children. Bennetts and Chapman found that pregnant ewes pastured on certain ground in Australia developed a macrocytic hyperchromic anemia and tended to produce lambs afflicted with swayback disease; when the anemia was treated prophylactically with iron, the incidence greatly decreased. Later, they found that [1] this improvement was due not to the addition of iron to the diet of the pregnant ewes but to its contamination with copper and [2] copper addition alone in the form of copper licks produced a great reduction in incidence. In 1948, Innes[2] made a similar study in England where he found that the specific anemia was not always present in the pregnant ewes and concluded that the disease could not be a copper deficiency per se, even though copper levels were usually low in affected sheep and lambs, because it occurred in areas in which the copper content of the pasture and soil was normal. They suggested that sheep might be unable to use the copper in the pasture and drew attention to the work of Dick and Bull[3] showing that molybdenum depresses copper metabolism and that, conversely, copper will cure the dysentery caused by excess molybdenum.

It is interesting to note further that swayback disease is endemic in England in areas around old leadworkings such as Derbyshire, which is an area well mined for lead. In cases of swayback disease in this area, Campbell[4] found a high lead content in the brains and livers of ewes and lambs, a finding which did not occur in the Australian cases. Thus, it would appear that in swayback disease a complex relationship among at least three, and probably more, trace elements exists which, when disturbed, might render the ewe and its lambs susceptible to demyelinization in the cerebral hemispheres. In Canada, as far as it is presently known, swayback disease is present only in a mild form in an area north of Lethbridge, Alberta; here it has been treated successfully by the administration of copper sulphate.

Campbell,[5] in 1948, suggested a possible connection between the geographic incidence of disseminated sclerosis and swayback disease. He investigated cases of disseminated sclerosis in Oxfordshire, Buckinghamshire, Berkshire, Cornwall, Suffolk, and Derbyshire in England. The average incidence in these areas was 20 per 100,000 of the population. However, in the Bakewell district in Derbyshire, where swayback disease is most common, the incidence was as high as 56 per 100,000. The relationship between the two diseases is nevertheless very tenuous. Later work by Campbell[6] showed that the cases of disseminated sclerosis had a tendency to group. Thus, Crowthorne in Berkshire with

From the Department of Medicine, Queen's University, and the Kingston General Hospital, Ontario.

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a population of about 200 and Whitney with a population of 600 each had 6 cases, an incidence considerably higher than average for the areas. Investigation of the soil around one of the Berkshire villages with a high incidence of disseminate sclerosis disclosed that the lead content in this area varied from 9 to 20 parts per million as compared with the normal content of 1 to 2 parts per million. Campbell makes the tentative observation that the disease seems also to be more common in the areas of high limestone content in England and draws attention to the close relationship between the metabolism of calcium and lead. It is interesting that a greater amount of lead was found in the teeth of many of his cases of disseminated sclerosis than was found in control groups.

If, in fact, cases of disseminated sclerosis do tend to group and to occur in small areas with a much higher incidence than the overall incidence in a country or county, this is a finding of the utmost importance. The present study was undertaken with the idea of determining whether [1] a similar grouping of cases of disseminated sclerosis could be found in a small area of Ontario and [2] if this grouping was found, any relationship between the grouping and the mineral content of the soil and water of the areas studied existed.

INVESTIGATION

The area surveyed was roughly a semicircle of 60 miles' radius, centered at Kingston. Included in this area were Leeds and Prince Edward counties and parts of Northumberland, Lennox and Addington, Frontenac, Lanark, and Grenville counties. The population of each county was obtained from the 1941 census; the populations of all the towns of over 2,000 persons were subtracted from the total of these county populations, and the populations of those towns which fell within our radius were added separately. The remainder, which may be considered the total rural population, was then converted into the density population per square mile. It was then possible to estimate the total rural population within our area, which was 91,400. It will be seen that these calculations assume a uniform density of population throughout the various counties. This is certainly not the case since the northern part of our area is bushland and sparsely populated. However, no alternative appeared possible with the census data available. We hoped that the discrepancy would be lessened by excluding the larger towns found mostly along the lake shore.

Prince Edward county has the densest rural population, with 32.9 persons per square mile; Frontenac, Lennox and Addington, Lanark, and Northumberland are the most sparsely populated, with populations of 12.78, 12.87, 12.89, and 12.91 persons per square mile, respectively. The discrepancy between these figures is due to the fact that Prince Edward county lies entirely around the fertile lake shore and is densely settled.

The total population was determined by adding the sum of the populations of all the towns of over 2,000 persons within the area to the total rural population; the total was 176,300. There are 3 large towns within our radius—Kingston, Belleville, and Brockville, with populations of 30,126, 15,710, and 11,342, respectively. Kingston, in Frontenac county, has both military and academic connections, being the headquarters of various Army establishments, the Defense College, and the Royal Military College and the seat of Queen's University. This means that it has a considerable floating population.

We attempted to contact every person with disseminated sclerosis who had lived within this semicircle before and at the time of onset of disease. Since the initial object of this study was to relate areas of higher incidence with an analysis of the soil and water content, we were not primarily interested in those persons moving into our area after the onset of disease. Any significant grouping would have to depend only on those cases living in our area at the time of study and those that had moved away before or after their disease symptoms had started. The former group were relatively easy to contact, but the practical difficulties of contacting persons who may have moved to any other part of the North American continent from our semicircle, before or soon after the first symptoms of their disease occurred, made it almost impossible to obtain reliable figures for the latter group. We were, however, able to trace 11 of these persons who were included in the hope that they might

nevertheless add weight for or against any grouping that should be present. Although it was only of secondary importance, we also determined the place of residence of persons having disseminated sclerosis who had contracted the first symptoms of their disease before moving into our area.

All of the 212 general practitioners in the area investigated were sent a circular letter with prepaid reply or else were contacted personally. They were asked for the names of any patients seen in the last ten years in which the diagnosis of disseminated sclerosis had been entertained. The names of 30 patients of whom we were otherwise unaware were obtained from the 85 doctors replying. An additional 51 names were found in the records of the local hospitals; 406 names were supplied from the records of Ottawa, Toronto, Belleville, and Brockville hospitals. The Toronto Branch of the Multiple Sclerosis Society of Canada contacted 110 of their members and had replies from 65. The Montreal General Hospital and the Montreal Neurological Institute each supplied the name of one case known to live in our district. To these names were added a number from our own private notes. After checking for duplication, a final list of 474 patients was compiled. All these people were then sent letters asking for help and, in particular, for details as to their previous places of residence; 199 replies were received. These replies were then scrutinized and 79 of those replying appeared to meet the requirements of having lived within the designated radius at some time before, or at the time of, onset of the first symptoms of their disease.

These 79 people were visited and examined, and a final list of 68 patients was made. Those excluded either failed to fulfill residential requirements or were not clearly cases of disseminated sclerosis. Of these 68 patients, 57 were living within our area at the time of examination and 11 had lived within our radius before or at the time of onset of the symptoms but were now living outside the area. Those persons moving into our area after the initial symptoms were not included. A map showing the site and approximate duration of residence within our area for every case was made (Figs. 1 and 2). It will be seen from this map that no very striking grouping occurs, although Kingston appears to show a higher incidence than either of the other two large towns or the rural population.

The 57 cases now residing within our district are shown in Figure 3. Of these, 37 are now living in towns of over 2,000 inhabitants and 20 are residing in villages or in the country. By reference to the map, it will be seen that our findings do not show the type of grouping in small communities found by Campbell in England. The rural cases were scattered uniformly near the shore line of Lake Ontario where the population is densest; an inland grouping appeared around Perth, a small town of 4,458 inhabitants in Lanark country. This town is situated in a valley running north and is more densely populated than the rest of the inland area; 3 patients here and 1 on a farm a few miles away developed the disease.

It is obviously impossible to make any calculation of prevalence from our figures. The incidence of disseminated sclerosis in our area could have been estimated in one of two ways: either we could enumerate every patient who had developed the first symptoms of disseminated sclerosis while living in our area or we could enumerate all cases of the disease living in our area at the time of our survey, including the established cases who had moved into the area. However, as we were so unsuccessful in contacting patients who had developed their first symptoms while in our area and subsequently moved away, no reliable incidence figures can be estimated in this way. With regard to the second possibility, the aims of the study were not directed to include any patients with disseminated sclerosis who had moved into our area after the disease had started.

Nevertheless, it appears to us that information of some value can be obtained by examining our figures. It must be clearly understood that our reference to prevalence bears little relationship to true prevalence and refers to figures with the limitations mentioned above. It can be said, however, that our prevalence figures, based on the number of patients who developed the initial symptoms of disseminated sclerosis while living in our area and who were still living there at the time of the study, represent an absolute minimal prevalence rate. Thus, from the 57 cases residing within our district at the time of study, a prev-

Figure 1

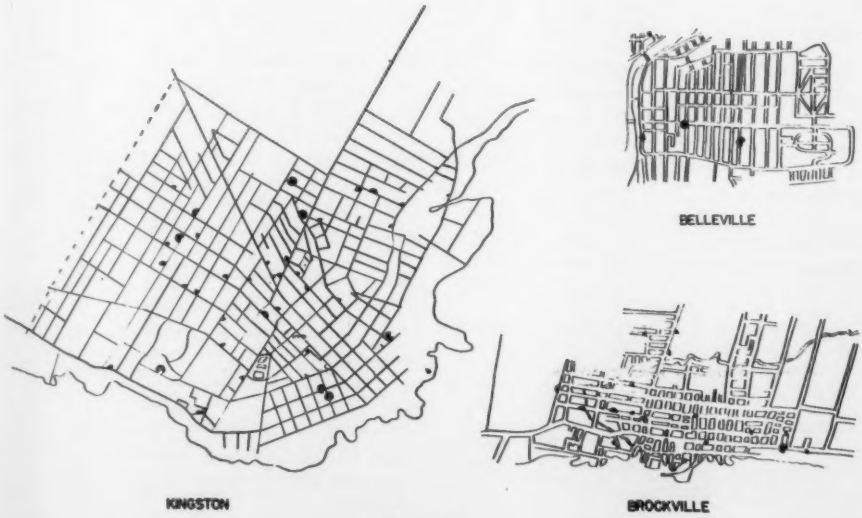


Figure 2

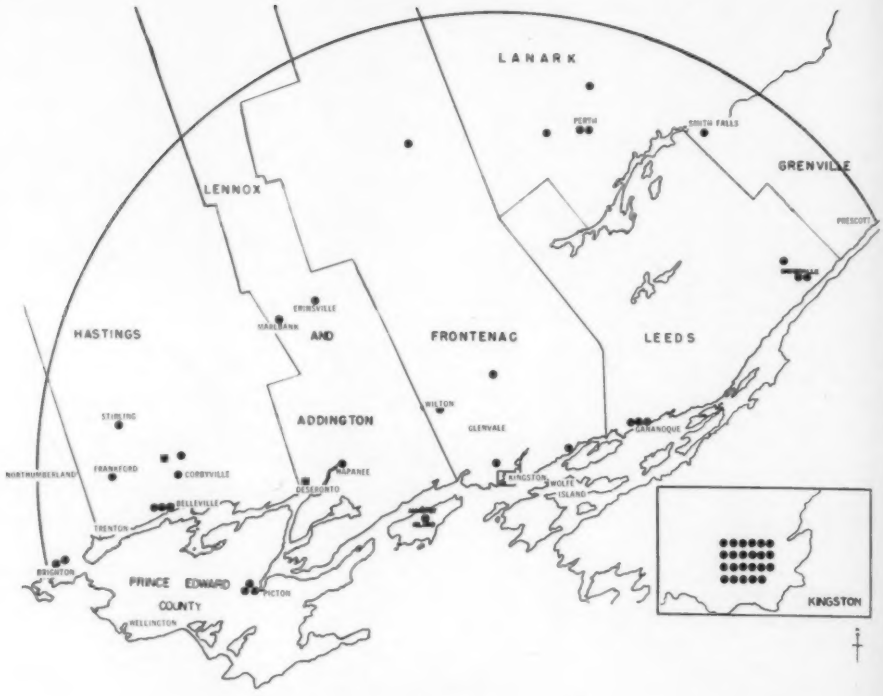


Figure 3

alence of 30 cases per 100,000 population was calculated. Of these 57 cases, 23 are now living in the Kingston area, giving us a strikingly high prevalence of 77 per 100,000. This variation from the over-all prevalence is statistically highly significant. This figure of 23 patients is somewhat misleading, however, because 5 of them are living in chronic hospitals and institutions because they have disseminated sclerosis and 1 patient is a student who does not properly reside in Kingston except during term time. Even if we correct for these 6 patients and reduce the number of the cases now residing in Kingston to 17, we still have a prevalence of 57 per 100,000 population, again a statistically significant variation from the over-all prevalence of 30 per 100,000.

TABLE 1

DISTRIBUTION OF 68 PATIENTS IN KINGSTON AREA AS TO CERTAINTY OF DIAGNOSIS

	Number of patients
Group 1 (certain)	47
Group 2 (probable)	6
Group 3 (possible)	7
Group 4 (uncertain)	8

CLINICAL INVESTIGATION

The 68 cases were subjected to a detailed history and physical examination, after which they were graded into 4 groups (Table 1) according to our judgment of the certainty of the diagnosis. To be included in group 1, termed *diagnosis certain*, the patient had to have at least 5 out of 7 diagnostic criteria—remittent history; characteristic symptoms; optic atrophy with scotoma; nystagmus, action tremor, dysdiadochokinesis, or incoordination;

signs of a pyramidal tract lesion; signs of a posterior column lesion; and definite and well-marked euphoria.

The other three groups were called *probable, possible,* or *uncertain;* made up of patients with 4, 3, or 2 of the above diagnostic criteria. Each case was, however, reviewed in the light of the whole illness, since occasional patients did not lend themselves to classification by such rigid criteria.

CASE STUDIES

A brief summary of the history and physical findings of one patient from each of these 4 groups follows.

Case 1 (Group 1). In November 1946, at the age of 22, this man, then in the Navy, had a transient episode of frequency of micturition and nocturia. In May 1948, he had a series of attacks of paresthesias and numbness affecting the chest and abdomen and later the right leg, which, in addition, became weak. The right leg began to improve after two weeks and then relapsed when the left leg and hand also became weak and numb. This weakness and loss of sensation were accompanied by clumsiness and tremor on action. One month later, he found that the vision of his left eye was blurred; this deteriorated over two days until he could only distinguish light from dark. As the vision improved, he noted that the eye was immobile and he would occasionally experience diplopia. He also complained of tripping over his words.

On examination at this time, he was markedly euphoric, laughed extremely easily, and had early bitemporal pallor of both optic disks and a large, left central scotoma. There were gross nystagmoid jerks of both eyes, particularly marked on looking to the right, of the type described by Wilfred Harris as ataxic nystagmus. In addition to these oculomotor signs, a total left sixth nerve palsy was noted. His speech was syllabic and staccato. Very marked terminal action tremor in the right arm with accompanying dysmetria and incoordination and slight bilateral dysdiadochokinesis were present. There was no spasticity, and his deep reflexes were not accentuated, but both plantar responses were extensor. His gait was ataxic. Vibration sense was impaired in both legs and in the right arm. Cerebrospinal fluid determination showed 7 white cells per cubic millimeter with 32% protein and a slightly tabetic gold curve.

Within two weeks, these symptoms largely cleared, although his legs remained too weak to allow him to work. Five months after this episode, his left leg again became numb, with paresthesias and weakness; this subsequently improved, but, later, the vision of the right eye became impaired and diplopia occurred. On examination at this time, the patient was still euphoric; the temporal pallor of both optic disks was now well marked, and there were central scotomata in both eyes. He still showed gross nystagmus, this time largely of the rotary type, with incoordination and pyramidal and posterior column signs as before. These symptoms improved, but 4 similar episodes have subsequently occurred with increasing residual disability each time. He now shows less marked, but still definite euphoria, alternating with periods of depression; gross pallor of the optic disks; gross nystagmus in both horizontal and vertical planes; coarse terminal action tremor, particularly marked on the right side, with other signs of incoordination affecting both arms; and a spastic, ataxic gait without gross accentuation of his deep reflexes but with absent abdominal and cremasteric reflexes and extensor plantar responses. There is loss of vibration sense in both legs and mild loss of joint position sense in his toes.

Case 2 (Group 2). This 46-year-old man gave a poor history of episodes of painful, swollen joints since the age of 21. At the age of 42, he noticed weakness in his legs, especially the right; this progressed without remission. Over the same period, he found his hands were less powerful and unable to perform fine movements. Associated with these motor symptoms was a numbness over the left face and body.

He was an anxious man with marked lability of mood and euphoria. He had no pallor of his disks and no scotomata, but there was a well marked rotary nystagmus on conjugate horizontal deviation and moderate weakness of all his limbs, most marked on the left and especially affecting his grip and movements of the ankles. The tone was not noticeably increased in his arms, but his legs were spastic and all his deep reflexes were exaggerated; the left plantar response was extensor and the right equivocal. There was slight dysmetria with the left hand but no obvious incoordination or action tremor. Vibration sense was markedly impaired over the left leg and arm and joint position sense impaired in the left fingers. He had a spastic ataxic gait, of stamping type with stiff legs.

Case 3 (Group 3). In March, 1950, this 26-year-old girl began to experience dizziness when at her work and complained that her vision became blurred in both eyes. Later that day, she noticed that she could not walk straight and was falling to either side. She was feeling nauseated by this time and vomited her food for the next two days. She also experienced difficulty in feeding herself and, when lighting her cigaret, was particularly clumsy with her left hand. She was dysarthric.

On hospital admission a day later, both of her legs were weak and she was suffering from frequency of micturition. A frontal headache mostly on the left side was experienced at the start of the attack, but it disappeared shortly afterward. Her vision became clear, and her other symptoms disappeared one week after the attack began. Six

TABLE 2
NATIONALITIES OF 68 PATIENTS STUDIED

Nationality	*Total number of patients*	*Group 1 patients only*
British Canadian	59	41
Scottish	3	1
English	3	3
French Canadian	1	0
Ukrainian	1	1
German Jew	1	1

weeks later she had another attack of vertigo of one day's duration.

The patient revealed a left paracentral scotoma, no definite edema or pallor of her optic disks, and slight horizontal nystagmus on looking to the left. Weakness of the muscle power in her left arm and leg, absent abdominal reflexes, and increased knee and ankle jerks on the left were noted. Impaired vibration sense in the right wrist and impaired joint position sense in the left leg were apparent. Dysmetria, dysdiadochokinesis and action tremor were more marked in the left arm and leg than on the right.

Case 4 (Group 4). A healthy 16-year-old girl developed a cold in the head, followed by occasional diplopia. Two weeks later, she was admitted to an isolation hospital with an unproductive cough and no fever; after two more weeks, she complained of inability to swallow and was admitted to a general hospital. On examination at that time, she displayed horizontal nystagmus, absent abdominal reflexes on the left, bilaterally increased reflexes more marked on the left, bilateral extensor plantar responses, and bilateral ankle clonus. Her cerebrospinal fluid showed an increased protein content of 72 mg. per 100 cc., with a tabetic curve. Two years later, in 1949, inquiry revealed that she had suffered from no further episodes and neurologic examination revealed no abnormality.

ETIOLOGIC FACTORS

Of the 68 cases in our study, 29 were men and 39 were women; 19 men and 28 women were classified in group I. This sex distribution has not often been remarked by other workers but appears to be in accord with the survey recently made by Kurland.[7]

One case of familial incidence was encountered—a 44-year-old mother developed the disease at the age of 26, and her son, now aged 24, had his first symptom at age 23. Both had paresthesias as initial symptoms but were not otherwise similar. The son was delivered by forceps as the mother had toxemia of pregnancy.

Differences in nationality are shown in Table 2. The occupations are shown in Table 3; from this it can be seen that 12 patients were engaged in open-air employment and 56 worked indoors. Living predominately in the town before the onset of their disease were 48 patients; 20 were country dwellers. Steiner[8] in studies in Germany and Scotland had shown a preponderance of rural cases over urban. Our figures apparently suggest just the reverse.

Table 4 shows the total number of patients whose symptoms started in each decade and the numbers of patients classified in group I with symptoms originating in each decade.

Where the subject could be tactfully raised, inquiries were made regarding income. Table 5 shows this information from the 55 patients who replied. The average monthly salary in Ontario for December 1949 was $196.00 per month. A glance at Table 5 reveals that only

TABLE 3
OCCUPATIONAL DISTRIBUTION OF 68 PATIENTS

	Number of patients	
	Male	*Female*
Housewife		24
Farmer	7	
Clerk	5	
Nurse		5
School teacher	1	3
Shop assistant	1	2
Student	2	
Stenographer		2
Chemist	2	
Truck driver	2	
Hardware polisher	1	
Fur blocker	1	
Weaver	1	
Foreman	1	
Signal man	1	
Switchboard operator	1	
Shoe factory worker	1	
Tilepacker		1
Sales manager	1	
Laborer	1	
Artist		1
Social worker		1
Total	29	39

TABLE 4
DECADES IN WHICH INITIAL SYMPTOMS PRESENTED

Age of onset	*Total number of patients*	*Group 1 patients only*
0 to 10	–	–
11 to 20	12	11
21 to 30	21	15
31 to 40	26	17
41 to 50	8	3
51 to 60	1	1

16 patients earned more than the average income and that the salaries of 39 were well below this. The estimated average income was $173.00 per month. This finding is not considered significant because the average monthly salary figure will include a few earners whose income is very high and which will raise the average. Our group, however, was too small to make inclusion of one of the few high earners likely; indeed we see that the highest income in our group was $400.00 a month. For this reason we believe that the difference in income between our group and the Ontario average is not a valid one. It also appeared that the proportion of unmarried persons, especially women, was higher in our group than in the general population; this would act as a further factor lowering the average income in our group below the general population's.

The weights and heights of 66 patients of the series were obtained. The usual weight of the patients before onset of illness was compared with the figures listed by the Committee of the Association of Life Insurance Directors and Actuarial Society of America as average weights for men or women of corresponding age and height. From a comparison with these figures, it was noted that 44 of the patients were underweight at the onset of their illness, one by as much as 46 lb. The average number of pounds underweight was 16; this would seem to be in accordance with the findings of Brickner and Brill.[9] One patient was 28 lb. overweight, being the heaviest of 16 patients weighing more than average at the onset of their disease. The average number of pounds overweight was 14. These figures would not appear to us to be very significant.

Swank[10] at the Montreal Neurological Institute has recently reported an association between high fat intake and the onset or exacerbation of the disease and claims improvement on an exceedingly low fat diet. Crane[11] has made similar but precisely opposite observations in which he found a low fat intake in patients with disseminated sclerosis and claims improvement in most of his cases put on a high fat diet. Inquiries about our patients' diets revealed that 18 of the total series of 68 patients had dietary fads: 11 had aversions to fats in the form of fatty meat, eggs, milk, and greasy foods; the other 7 had fads including parsnips, squash, cabbages, cauliflower, turnips, bread, cornflakes, potatoes, rolled oats, onions, and sea food. Special inquiry was made for food aversions or dietary changes before the onset of the disease or its relapse. In not one case was such a story given. We believe that these findings are probably in accord with the dietary fads of the healthy population.

Specific inquiries were also made in every case regarding the relation of the onset of symptoms, relapses, and remissions to the history of injury, infection, pregnancy, allergy, thyrotoxicosis, metallic poisoning, or other disease. No history of infection within three months of onset or remission was encountered except from 2 patients—1 was in the uncertain diagnostic group and had a high fever at the time of disease onset in addition to a history of preceding explosion and possible metallic poisoning; the other case had a history of acute upper respiratory tract infection,

TABLE 5

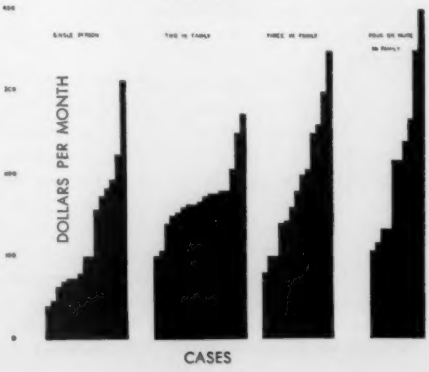


TABLE 6
FREQUENCY OF OCCURRENCE OF INITIAL SYMPTOMS OF DISSEMINATED SCLEROSIS

Symptoms	*Total number of patients*	*Group 1 patients only*
Weakness of one or both upper or lower extremities	20	13
Numbness	11	10
Blurring of vision	10	7
Diplopia	10	9
Bladder symptoms	5	2
Ataxia	5	3
Complete blindness	3	3
Dysarthria	1	0
Difficulty in swallowing	1	0
Ocular paresis (without diplopia)	1	0

followed two weeks later by vertigo, diplopia, dysphagia, and ataxia (case 4).

Including the patient mentioned above, there were 8 patients (12%) with a history of antecedent trauma; 3 of our patients developed an exacerbation of preexisting symptoms after trauma.

SYMPTOMS

The initial symptoms of the disease and frequency of occurrence are enumerated in Table 6. The number of cases falling into group 1 who showed these symptoms initially are also indicated; from this comparison it can be seen that the same distribution obtains. Symptoms complained of during the course of the disease are shown in Table 7. The four commonest complaints are paresthesias, weakness, bladder disturbance, and visual and ocular dysfunction.

In view of the opinion expressed by McAlpine,[12] Thygesen,[13] and McIntyre and McIntyre[14] that many cases of typical disseminated sclerosis do not show a remittent history, inquiry was directed toward the dates and duration of relapses and remissions. Any period during which the symptoms formerly present improved or disappeared was considered as a remission. A relapse was a period when the symptoms formerly present became worse or new symptoms appeared. In this connection, it must be borne in mind that clear-cut relapses are not easy to distinguish once the disease is well established; moreover, patients' memories may not be wholly accurate in distinguishing date of onset of one symptom from another, and a tendency probably exists for the disease, once several years have elapsed, to be recalled as a progressive whole. With these restrictions in mind, a chart was prepared showing the progress of each case (Table 8). From this it appears that of the 68 cases, 51 patients experienced remissions, while 17 appeared to be progressive from the start. It also appeared that in all cases where the disease had lasted for several years, there was a tendency for it to become progressive and remissions to disappear. This last observation is no doubt due to the difficulty in distinguishing remissions, once the disease has become widespread and well established. Of the 51 patients showing remissions, 22 had more than one; 11 of these showed a tendency for the duration of the remission to become

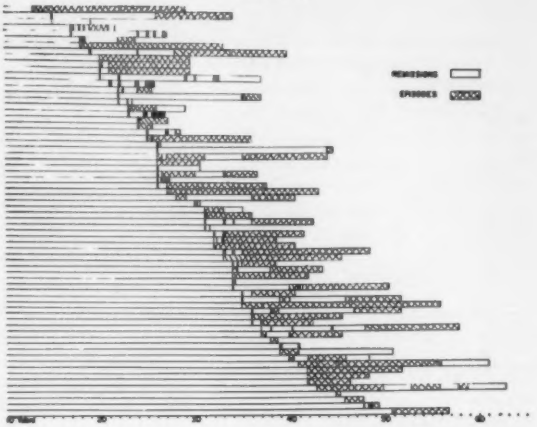
TABLE 7
FREQUENCY OF OCCURRENCE OF SYMPTOMS DURING COURSE OF DISEASE

Symptoms (in order of frequency)	*Total number of patients*	*Group 1 patients only*
Numbness or tingling	55	42
Weakness of one or both lower extremities	54	42
Bladder symptoms	(90)	(76)
Urgency	39	35
Frequency	8	2
Retention of urine	2	2
Incontinence	38	34
Delay in starting micturition	3	3
Blurred vision	33	21
Diplopia	24	18
Vertigo	17	14
Low back pain	13	5
Impotence	10	9
Headaches occurring at or just before onset	7	4
Nausea	5	4
Tinnitus	4	3
Defective memory	4	3
Hyperalgesia	2	2
Loss of rectal control	2	2
Seizures	2	1
Girdle pain	1	1

shorter as the disease progressed. Remissions of over five years' duration were experienced by 8 patients, the longest being of eighteen years' duration; 3 patients underwent remissions of as long as sixteen, seventeen, and eighteen years after the first symptoms of disease had appeared. Thus, the tendency for the disease to become steadily progressive as it advances has very definite exceptions.

If we assume that there are two types of disease—the progressive and the remittent varieties—it is possible to contrast these two as far as our patients are concerned (Table 9). We are not willing to draw any deductions from these tables nor to infer that the two varieties, if they occur, differ either in rate of progress or in severity. It appears to us that these tables merely show that the longer the illness has been present, the more severe is the disablement likely to be.

TABLE 8



In considering the relationship between remissions and symptoms, perhaps more information is to be found. Transient attacks of blurring of vision had been experienced by 33 patients, 10 at onset and 23 during the course of disease. In all but 4 of these 33

TABLE 9

PATIENT DATA FOR PURPOSES OF CONTRASTING THE REMISSIVE AND CHRONIC PROGRESSIVE VARIETIES OF DISSEMINATED SCLEROSIS

REMISSIVE TYPE

			Duration of illness and Stage of Disablement			
Age at onset	*Male*	*Female*	*None or Slight (Months)*	*(Years)*	*Moderate (Years)*	*Severe (Years)*
10 to 20	2	7		5, 5, 6	8, 10, 20	11, 11, 21
21 to 30	9	10	3, 6	2, 3, 3, 5, 15, 19	3, 3, 5, 10, 10, 13, 21	6, 12, 17
31 to 40	10	10	2, 6, 6	2, 3, 6, 8	5, 5, 5, 6, 6, 9, 11, 12, 17	6, 9, 15, 21
41 to 50	2	1			21	2, 21
51 to 60						

CHRONIC PROGRESSIVE TYPE

Age at onset	*Male*	*Female*	*None or Slight (Years)*	*Moderate (Months)*	*(Years)*	*Severe (Years)*
10 to 20	–	3				10, 16, 17
21 to 30	1	1	1		5	
31 to 40	3	3	10		10	7, 11, 16, 22
41 to 50	2	3	25	9	7, 9	
51 to 60	1	–	1			5

patients, blurring cleared completely. Onset of the blurring was sudden in 24 patients, and both eyes were affected in 25 patients; 4 persons became temporarily but completely blind to all light in one or both eyes at the onset or during the course of the illness. These attacks were short in duration, lasting from a few hours up to three months. The number of episodes of impaired vision experienced by each person varied from 1 to 2, and the length of time from an episode of blurred vision as an initial symptom until the disease was fully established was less than two years in 3 patients, less than five years in 3, and more than five years in 4. The longest period was eleven years. This agrees with the findings of McIntyre and McIntyre[14] who commented on the good prognosis of retrobulbar neuritis as an initial symptom. The prognosis for the individual attack would also appear to be good.

TABLE 10
PHYSICAL SIGNS OCCURRING WITH DISSEMINATED SCLEROSIS

Symptoms (in order of frequency)	*Total number of patients*	*Group 1 patients only*
Abdominal reflexes diminished or absent	57	47
Extensor plantar response	54	47
Dysmetria and dysdiadochokinesis	48	40
Optic atrophy	48	39
Ataxia	47	40
Deep reflexes in lower extremities increased	44	39
Involvement of posterior columns	43	34
Action tremor	37	32
Nystagmus (34)	(14)	
Horizontal and vertical	18	3
Rotary	4	2
Horizontal	7	7
Nystagmoid jerking	5	2
Spastic gait	32	29
Ankle clonus	31	22
Emotional instability	25	22
Speech disturbance	25	16
Cranial nerve involvement (37)	(26)	
External rectus	12	11
Dysphagia	6	5
Ptosis	3	2
Cochlear nerve	3	1
Internal rectus	8	5
Facial weakness	3	2
Tongue deviation	2	0
Mild changes in pain, temperature and touch sensation	13	8
Abnormalities of pupil reaction (2)	(1)	
Sluggish reaction to light	1	0
Irregular pupils	1	1

Of the 54 cases who developed weakness of an extremity during the course of the disease, 23 experienced remissions in the weakness at some stage. Unlike the complete remissions of disturbance of vision and ocular paresis with no appreciable remaining disability experienced by our patients, the symptoms of weakness cleared up completely in only half of these cases. In the other half, the weakness improved only slightly or remained unchanged. The length of time between episodes of limb paralysis varied from a few months to two years, although limb weakness cleared up completely and did not recur for seven years in 2 women. The length of time between an initial episode of limb weakness and well established disease was under two years in 18 of 23 cases; in the 5 others, it was three, four, four, seven, and ten years, respectively. Thus, an episode of limb weakness would appear to herald a more rapid deterioration than when the disease starts with ocular symptoms.

Complete remission of numbness or tingling occurred in 33 of 55 patients so affected; this symptom heralded the disease in 10 patients and occurred during the course of disease in 45. The episodes lasted from one day to six months and, in 12 cases, were followed by the onset of weakness in the same limb. The time which elapsed between the appearance of numbness and tingling and the onset of weakness or other symptoms was usually from one to two years, although, in one patient, the onset of paresis was delayed for eighteen years; 11 patients suffered from more than one clear-cut episode of numbness in the same limb.

When many relapses occurred at frequent intervals at an early stage in the disease, the deterioration of the patient was very rapid. There were 8 such patients in our study; in 1 with widely spaced remissions the illness had lasted nineteen years, but, in the remaining 7, the illness had lasted only one to seven

years. Only 1 of these 7 patients was still able to work; one other, with illness of seven years' duration, was completely confined to bed.

No evidence presented to suggest that the course of the 9 patients who developed the disease after 40 years of age was different in severity or rate of progress from any of the other age groups. This impression contrasts with that of McAlpine[12] who stated that the older the patients, the more localized the signs and the more chronic the course of the disease.

We are, however, in agreement with McAlpine's finding that retrobulbar neuritis and euphoria are uncommon in such patients; among these 9 patients, only one had retrobulbar neuritis occurring at the onset of the disease and none with euphoria.

Physical Signs

The signs in order of frequency of occurrence are shown in Table 10. No essential difference exists between those cases which fall into group 1, in which the diagnosis was reasonably certain, and the cases as a whole. It is because of this correspondence, which was also noted in the initial symptoms and in the symptoms experienced up to the time of examination, that we believe that we were fairly successful in establishing the diagnosis of all our cases, even in those which fell into groups 2, 3, and 4. If conditions other than disseminated sclerosis had been included in this whole group, it would be expected that fairly significant differences would appear in an analysis of symptoms and signs between the group in which the diagnosis was considered certain and the total group.

Table 10 further shows that the commonest signs are those of various manifestations of pyramidal tract damage. These are closely followed in frequency by evidence of optic atrophy, cerebellar incoordination, and posterior column damage. Nystagmus, surprisingly, appeared ninth on the list.

The disease usually manifested itself as weakness of an extremity, progressing slowly or intermittently to culminate in a spastic paralysis. In our series, there are 32 patients with spastic quadriplegia, 12 with paraplegia, 9 with hemiplegia, and 2 with monoplegia.

Examination of the optic disks revealed two abnormalities—pallor of the temporal side of the optic disk and slight pallor of the disk in its entire extent. There were 26 patients showing the former and 3 the latter.

Abnormal findings in the fields of vision were peripheral constriction of the visual field evidenced in 7 patients and central or paracentral scotoma in 32. Of the 7 patients exhibiting peripheral constriction, 4 had no abnormality in their optic disks, which led us to suspect the validity of this sign; 1 showed uniform pallor of the disks; and the 2 others had pallor of the temporal sides of both disks. Impaired visual acuity without any appreciable change in optic disks was shown in 5 patients with histories of visual disturbance.

Signs of cerebellar incoordination in the early stages of the disease, either at the onset or in the first two years, were manifested in 16 patients; of these, 3 were bedridden at the time of examination—1 within a year of onset, 1 in 5 years, and 1 in 8 years. Moderate to severe disability was evidenced in 10 patients; 3 of these had deteriorated very rapidly from onset of the disease in a space of one to three years. Of the other 3 patients showing signs of incoordination as an early feature, 1 had experienced a second episode of short duration and now, two years from the onset, was free of symptoms; the other patient with signs of incoordination had suffered another episode of paresis and was very slightly disabled three years after onset; and the last case was recovering from the first episode.

Although it would seem from these cases that the onset of incoordination at an early stage in the disease might be a bad prognostic sign, it must be noted that this type of disability is in itself severely crippling and causes severe restriction of the abilities of the patient.

There were 14 patients who exhibited the triad of Charcot, but only 3 developed the classical signs of nystagmus, scanning speech, and intention tremor at the onset of the disease. The other patients showing these signs were rapidly progressive cases; 6 were bedridden after a period of time varying from one to ten years, and 5 were severely disabled and were just able to get about. These cases showed signs of Charcot's triad after variable intervals of one to ten years from onset of illness. The triad of Charcot, therefore, appears infrequent-

ly in the initial stages of the disease but could be demonstrated in the advanced stages in 20% of our series.

It was of course unjustifiable and impossible with our small series of patients to attempt any calculations regarding the average duration of the disease. It is interesting, however, that 6 patients had survived over twenty years since the onset of the illness; of these 6, 2 had first developed symptoms at the ages of 42 and 40, 2 at 37 and 34, 1 at 26, and 1 at 19. There was nothing very remarkable about the histories; 5 patients had the remittent type with either 2 or 3 episodes—3 of whom finally developed the chronic progressive type in five to ten years—and the sixth patient appeared to have the chronic progressive type from the onset. Disease had begun with weakness of one leg in 2 of these patients, with numbness in 2, and with blurring of vision in 2.

DISCUSSION

Clinically, there is nothing very remarkable about the type of cases in this study. The only point of any great interest emerging from this study appears to be a consideration of the geographic incidence of the disease. It will be remembered that against the over-all prevalence of 30 cases per 100,000 population for our whole area, Kingston, even when corrected for cases of false residence, showed a prevalence of 57 per 100,000—a variation which is statistically significant. In this connection, it should be recalled that numerous studies have been made in the last several years in which variations in the incidence of the disease between district and district have been emphasized. Incidence appears to vary not only between country and country but also between districts in the same country. In Denmark, Gram[15] found more cases in the middle of the Utland Peninsula and on the Island of Funan than elsewhere. Ackermann[16] noted that the incidence in Switzerland was very high. It ranged from 38.8 per 100,000 in North Switzerland to 3.1 per 100,000 in Wallis in South Switzerland. With the exception of the cantons of Moësa and Munsterthal, the incidence of cases in South Switzerland was very low compared with those in North Switzerland. Bing[17] confirmed this variation between North and South Switzerland and found that the relative proportion of cases was between 3 and 4 in the former area and 1 in the latter. In England, Campbell found an over-all incidence of 20 cases per 100,000 population and, in the county of Derbyshire, where the soil contained much lead, an incidence of 56 cases per 100,000. More recently, Swank[18] studied cases in Norway and reported a higher incidence around areas of the densest population.

Quite apart from these reported variations from district to district, it has, of course, for long been realized that very marked variations occur from country to country. According to Gabriel Steiner,[8] the disease is common in the northern states of Europe, Scandanavia, Germany, North and Central France, the Netherlands, Belgium, Austria, and Czechoslovakia. The disease is rarely found in Italy, Spain, and the Mediterranean coast of France and Romania. Brazil, Chile, and Japan are said to be free of the disease, while Woods in 1929 found that the incidence in China was two-fifths of that in Russia. Dean's latest figures[19] indicate that the disease is very rare in South Africa. The marked variations between the northern and the southern United States has also long been known; in 1922, Davenport[20] published figures showing that the maximum incidence of disseminated sclerosis was in the states of Michigan and Minnesota, each with an incidence of 18 per 100,000 population, while Wisconsin was the next highest with 14 per 100,000. Perhaps the most interesting information yet published has been that of Limburg[21] in his analysis of mortality statistics in North America, Great Britain, and Europe. His figures for North America show a very marked difference between the southern states and those states and provinces bordering the Great Lakes where the death rates for disseminated sclerosis are as high as 2.9 per 100,000 population in Manitoba and 2.0 and 2.3 in Minnesota and Iowa, respectively. Kurland,[7] however, has pointed out that these figures, although undoubtedly showing a real difference as compared with the southern states, are unduly weighted, since they include not only all cases in which the death certificate showed a diagnosis of multiple sclerosis or disseminated sclerosis but also all cases in which the diagnosis of cerebral sclerosis appeared. Since

many practitioners use the term cerebral sclerosis synonymously with cerebral arteriosclerosis, Limburg has obviously included some persons who did not die from disseminated sclerosis. Kurland goes on to show that when these cases of cerebral arteriosclerosis are discarded, the mortality curves for the northern United States, Canada, and Europe approximate very closely. However, even with this correction, there is a marked difference in the incidence of disseminated sclerosis between the southern United States and the northern United States and Canada.

It was because of these interesting differences in the regional incidence of disseminated sclerosis that we were encouraged to look at our own figures more closely. Especially, we were interested in the difference in prevalence between Kingston and the whole area.

It will be remembered that one of the sources from which we compiled our original list was the general practitioners in our area. These physicians were engaged mostly in the practice of surgery or midwifery and were therefore unlikely to come across such cases. Of the whole group of 212 doctors, 155 lived outside Kingston and were therefore approached by letter: only 50 of these 155 answered our letters. Of the 57 doctors living in Kingston, 22 were contacted by mail and 3 replied. All of the remaining 35 Kingston doctors were contacted personally or by telephone because these were known to be seeing medical patients; 100% of replies were therefore received. It is obvious that we were more successful in contacting the doctors in Kingston than those living outside. Moreover, of the doctors contacted in Kingston, replies were received from all who were likely to see such cases. Thus, the cases in our series were unduly weighted in favor of Kingston. Other factors must be added to this weighting:

- Kingston is the only town with a university hospital in our area and the only neurologist within our area also practices in Kingston. It is therefore probable that more cases of disseminated sclerosis will be recognized by the specialized personnel at the University Hospital in Kingston than in the hospitals elsewhere in our district.
- Patients requiring hospital investigation tend to be admitted to their local hospital; thus, more cases of early or doubtful disseminated sclerosis will be recognized in Kingston hospitals than in the hospitals of the surrounding district.
- Kingston has a higher number of doctors per unit population than anywhere else in Canada. The population is relatively small, and the medical school and teaching hospital located there raise the number of physicians. It is therefore more likely that early symptoms of the disease will be recognized here than in less heavily doctored areas.

We believe that these factors alone account for the very marked difference in prevalence shown in our study between those living in the area of Kingston and the area outside. A similar study was carried out in Rochester, Minnesota, in the area around the Mayo Clinic. There, in a town of 33,000 inhabitants, MacLean and workers[22] found 21 cases of disseminated sclerosis among the residents, making an incidence of 64 per 100,000 population, which is much higher than the 18 per 100,000 figure usually given for the incidence in the state of Minnesota. It will be noted that MacLean's study shows many of the same features reproduced in our own work. In a relatively small town, a large and highly specialized clinic is established; it would appear, therefore, that residents of the town of Rochester would find it relatively easy to get specialized attention as soon as neurologic symptoms occur and that this medical attention is more likely to result in a correct diagnosis than in towns without such a highly specialized center. This point is especially valid in a disease like disseminated sclerosis where the symptoms remit so that delay in obtaining medical attention may be accompanied by improvement or disappearance of the symptoms causing the patient to loose his intention of seeking medical help. It is apparent that both our study in Kingston and MacLean's in Rochester have been successful in drawing to the surface and diagnosing more cases of disseminated sclerosis than usually are diagnosed over larger and less heavily doctored areas. Further, it is very unlikely that MacLean or ourselves succeeded in discovering every case of disseminated sclerosis in the areas surveyed. This is especially true when the transient nature of many of the initial symptoms of this disease is consid-

ered. Furthermore, even in a heavily doctored urban area, there are still a number of people who refuse to call for medical aid at all or until late in the disease. Therefore, based on both MacLean's and our intensive studies of 2 small urban populations, the incidence would appear to be in the region of 60 per 100,000; nevertheless, it is probable that the true incidence of this disease is even higher. We would especially draw attention to the fact that our own figures are not those of true incidence or prevalence but are a minimal or subminimal estimate. It does not seem unreasonable to guess that, if all cases could be discovered, the true incidence of disseminated sclerosis around the Great Lakes would be near 100 per 100,000 population.

In any event, it is quite obvious that in intense studies of a small part of the population, marked variations in the apparent incidence between one area and another may occur. This brings into question not only the validity of the careful original work which inspired this study, but also the validity of those other pieces of work mentioned above which purport to show very marked variations in incidence between different districts in individual countries.

With regard to Campbell's studies, several criticisms may be made: First, he collected his cases by writing to doctors and asking them to notify him of patients with definitely proved disseminated sclerosis who had been resident in the area studied for at least two years. The work reported here has shown one result of uneven sampling, and this may well have occurred with the replies Campbell received. Also, in his case even more than with our own investigation, much depended upon the skill and enthusiasm of the doctor contacted. Obviously, a conscientious and skilled practitioner, in whose practice several cases of neurologic disease arise, will have taken the necessary steps to establish the diagnosis. Another less conscientious practitioner may neither have taken these steps nor have sufficient interest to reply to the investigator's questionnaire. Second, apart from these possible errors of sampling, Campbell only visited those cases in the vicinity of Oxford where he found the majority of diagnoses to be correct. Third, it does not appear that any note was made of the place of residence of the patient before

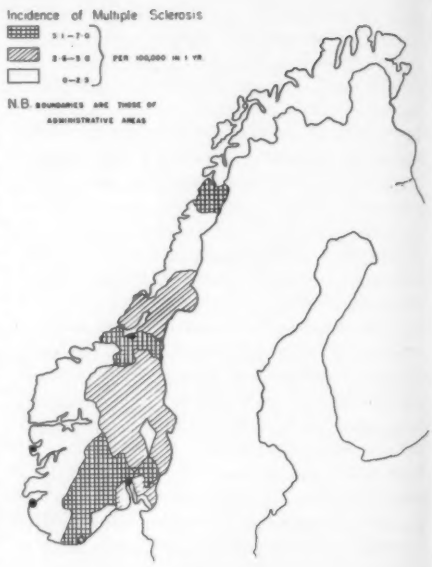


Figure 4

the illness commenced, so that some may have developed the illness before moving into the 6 counties investigated and others who developed the illness in the 6 counties may have moved out before the investigation was made. These latter objections, however, do not apply to those few villages which he has recently investigated in more detail.[6] In these villages, the diagnosis was verified in all the patients and the length of residence was similarly established.

It is even more interesting to examine the recent report of Swank and others[18] regarding the incidence of disseminated sclerosis in Norway in the light of the defects in such regional studies brought to light by the present work. Swank endeavored to survey the whole of Norway for cases of disseminated sclerosis. He claimed that this was easier than in other countries because one neurologic department in Oslo serves much of Southern Norway and neurologists in Norway have all had a similar training in this department. He also pointed out that cases giving rise to diagnostic difficulties were "referred to the University Hospital in Oslo." His survey was based on question-

Figure 5

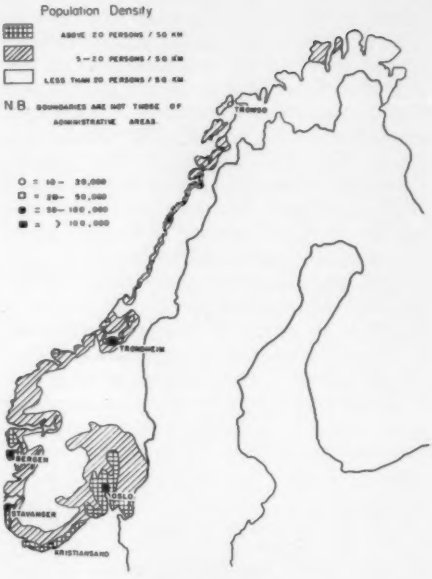


Figure 6

naires sent to all Norwegian hospitals and "many" neurologists. The response to these questionnaires was about "80 per cent complete." From this data, he constructed an incidence map (Fig. 4).

The replies to Swank's questionnaires were much more complete than our own, which would help to eliminate one source of error, but his inability to contact all the Norwegian neurologists might introduce fallacious results. Not all neurologists admit patients with disseminated sclerosis to hospital when the diagnosis is obvious from an office examination. Moreover, if the patient is either very slightly or very severely disabled, hospital admission may not be considered justifiable. The failure to contact even one neurologist in a sparsely populated area might have the most profound effects on the calculated incidence.

Of more importance, however, would be the communication facilities. However excellent the Norwegian neurologic diagnostic service may be, it is hard to see how patients with early stages of the disease living in the north of Norway or in the relatively isolated coastal fiord areas can easily travel to the neurologic diagnostic center or to the neurologist. Where access to one of the larger centers of population, such as Oslo or Trondheim, is easy by road or rail, it would obviously be easier to travel to a neurologist. The map showing Norway's road and rail communications (Fig. 5) will show that the areas of higher incidence shown in Swank's map (Fig. 4) correspond closely to areas where communications are well developed, with the single exception of the isolated area in Northern Norway. Swank points out, however, that the apparent high incidence in this latter region may be the result of the small sample (14 patients).

Finally, in a country such as Norway, although health insurance is compulsory, medical care still has to be paid in part by the patient. One cannot neglect the effect of poverty on the figures for the incidence of a condition which is not disabling in its early stages and which usually improves with the passage of time as do the early episodes. Swank concludes from his study that the incidence is higher in the areas of higher fat consumption. However, it is well known that dietary fat is closely related to income and the

poorer population cannot afford diets rich in fats. For these reasons alone, we would expect to find an apparently lower incidence of disseminated sclerosis in the more sparsely populated areas which are sparsely populated because they cannot support a high standard of living. The population density map (Fig. 6) shows the densest population—and thus, in a rural community, the more prosperous population—to be concentrated in the areas where Swank found disseminated sclerosis to have the highest incidence. It should be remarked that Swank's map of incidence of the disease is based on administrative boundaries so that the boundaries of his areas of higher incidence are slightly fallacious; this may explain why these areas apparently do not correspond more exactly in contour with the population density map not drawn from administrative boundaries.

CONCLUSIONS

The time is ripe for a critical evaluation of all those studies that have purported to show differences in incidence between various countries or parts of the same country. Especially we must examine those studies from which assumptions concerning the etiology of the disease have been made. Sometimes, these assumptions have led to the investigation of methods of treatment which may not be justifiable. It would appear to us that the nature of disseminated sclerosis is such that figures for its incidence over wide areas may be extremely difficult to determine and very misleading. The intensive study of small areas may perhaps be more accurate. These areas, however, would need to be carefully selected if they were to prove representative of the larger area or country as a whole.

SUMMARY

1. An attempt was made to contact and study all persons in whom the onset of disseminated sclerosis occurred while they were living within a given district.

2. No evidence was found within the district studied that areas of high prevalence occurred, except for the Kingston area.

3. This high prevalence in Kingston was further examined and thought to be due to errors in sampling.

4. The suggestion is made that similar errors may have occurred in other cases where variations in incidence or prevalence have been reported.

REFERENCES

1. Bennetts, H. W., and Chapman, F. E.: Copper deficiency in sheep in western Australia. Australia Vet. J. 13:138, 1937.
2. Innes, J. W. R.: Demyelinating disease of animals. Assoc. for Research in Nerv. and Ment. Dis. 28:75, 1948.
3. Dick, A. T., and Bull, L. B.: Some preliminary observations on the effect of molybdenum on copper metabolism in herbivorous animals. Australia Vet. J. 21:70, 1945.
4. Campbell, A. M. G.:, et al.: Disease of nervous system occurring among research workers on swayback in lambs. Brain 70:50, 1947.
5. Campbell, A. M. G.: Factors in aetiology of disseminated sclerosis. Bristol Med.-Chir. J. 65:54, 1948.
6. Campbell, A. M. G., Herdan, G., Tatlow, W. F. T., and Whittle, E. G.: Lead in relation to disseminated sclerosis. Brain 73:52, 1950.
7. Kurland, L. T.: Hearing before House of Representatives on H.R. 3205, March 20th, U. S. Govt. Printing Office 83289, 1951, p. 134.
8. Steiner, Gabriel: Multiple sclerosis; etiological significance of regional and occupational incidence. J. Nerv. & Ment. Dis. 88:42, 1938.
9. Brickner, R. M., and Braill, N. Q.: Dietetic and related studies on multiple sclerosis. Arch. Neurol. & Psychiat. 46:16, 1941.
10. Swank, R. L.: Multiple sclerosis; correlation of its incidence with dietary fat. Am. J. Med. Sc. 220:421, 1950.
11. Crane, J. E.: Treatment of multiple sclerosis with fat-soluble vitamins, animal fat and ammonium chloride. Connecticut M. J. 14:40, 1950.
12. McAlpine, D.: The problem of disseminated sclerosis. Brain 69:233, 1946.
13. Thygesen, P.: Prognosis in initial stages of disseminated primary demyelinating disease of central nervous system. Arch. Neurol. & Psychiat. 61:339, 1949.
14. McIntyre, H. D., and McIntyre, A. P.: Prognosis of multiple sclerosis. Arch. Neurol. & Psychiat. 50:431, 1943.
15. Gram, H. C.: Occurrence of disseminated sclerosis in Denmark. Ugesk. f. læger 96:823, 1934.
16. Ackermann, A.: Die multiple Sklerose in der Schweiz. Enquete von 1918-22. Schweiz. med. Wchnschr. 61:1245, 1931.
17. Bing: Die Multiplen Sklerose Einst und Jetzt: Tatsachen und Fragestellungen. Schweiz. med. Wchnschr. 62:1069, 1093, 1932.
18. Swank, R. L., Lerstad, O., Strøm, A., and Backer, J.: Multiple sclerosis in rural Norway; its geographic and occupational incidence in relation to nutrition. New England J. Med. 246:721, 1952.
19. Dean, G.: Disseminated sclerosis in South Africa; its relationship to swayback disease and suggested treatment. Brit. M. J. 1:842, 1949.
20. Davenport, C. B.: Multiple sclerosis. Arch. Neurol. & Psychiat. 8:51, 1922.
21. Limburg, C. C.: The geographic distribution of multiple sclerosis and its estimated prevalence in the United States. Assoc. for Research in Nerv. and Ment. Dis. 28:15, 1948.
22. MacLean, A. R., et al.: Multiple sclerosis in a rural community. Assoc. for Research in Nerv. and Ment. Dis. 28:25, 1949.

Clinicopathologic correlations in cervical spondylosis

G. Robert Nugent, M.D.

MUCH ATTENTION has been directed recently to the problem of cervical spondylosis, although the pathogenesis of this common disorder remains obscure. In a patient with signs and symptoms of cervical cord disease and roentgeno- and myelographic evidence of spondylosis, a cause and effect relationship appears reasonable. However, several inconsistencies and discrepancies are noted in the clinical and surgical observations made in patients with this disease that make the problem appear more difficult to resolve. The purpose of this paper is to emphasize that several different but interrelated factors are involved in the pathogenesis of cervical spondylosis, some of which are secondary to the osteophytosis and some of which are unrelated. Further information implicating the ligamenta flava is presented, and the clinical, roentgenographic, and surgical features of this factor are stressed. The clinical findings and problems of cervical spondylosis have been presented in some detail by Bradshaw,[1] and Clarke and Robinson.[2]

Despite the apparently obvious relationship of the osteophytosis and cord compression, several disturbing features of the disorder must be considered when discussing the pathogenesis of spondylosis:

- The degree of neurologic deficit is entirely unrelated to the roentgenographic findings as noted on plain cervical films. Neurologic deficit may be advanced, with minimal roentgenographic changes, or roentgenograms may show extensive degenerative disease, with few or no clinical signs of cord or root compression. The latter situation is by far the more common, and Bradshaw[1] indicates that "about 65 per cent of people over the age of 50 have such spondylosis without neurologic symptoms or signs."
- In some patients with clinical and roentgenographic evidence of spondylosis, an unimpressive degree of cord compression may be found when the spinal cord is exposed at operation even though a mass anterior to the cord has been identified, according to O'Connell[3] and Bradshaw.[1] In many instances, the cord is thinned out or humped over the anterior mass or the denticulate ligaments are noticeably tight; other times, however, there seems to be room anterior to the cord and the denticulate ligaments are not particularly tense.
- Often, operation does not provide clinical improvement despite the release of a compressed spinal cord by sectioning the denticulate ligaments. This point has been stressed by Brain, Northfield, and Wilkinson[4] and Clarke and Robinson.[2]
- Instead of a clinical syndrome corresponding to anterior spinal cord compression, as might be expected, cervical spondylosis may be associated with any symptom complex of cervical cord disease. At times, the clinical picture is primarily one of lateral or posterior column involvement.

In attempting to resolve these inconsistencies and discrepancies, the literature was examined with particular attention to the pathogenesis of the disorder. The review indicated that cervical spondylosis is a complex disorder and that 3 major factors act together to determine whether symptoms will develop from this degenerative process of the cervical vertebrae and intervertebral disks. These fall under the headings of [1] vascular, [2] connective tissue, and [3] mechanical factors. Admittedly, the groups overlap considerably.

From the Department of Neurosurgery, Duke University Medical Center, and the Veterans Administration Hospital, Durham, N. C.

Dr. Nugent's present address is the Department of Surgery, Division of Neurosurgery, College of Medicine, University of Cincinnati.

VASCULAR FACTORS

Brain,[5] writing on ruptured cervical disks, made several observations concerning the vascular involvement associated with disk disease that are pertinent to a discussion of cervical spondylosis:

> No doubt the earliest changes produced by a protruded intervertebral disc are circulatory and these must be important at all stages. The veins with their thin walls and low pressure are compressed first and since the flow in them is upwards an edema of the anterior or anterolateral region of the cord and some segments below the site of compression would cause symptoms related to these segments. Similarly, edema would be produced in the spinal roots compressed. Arterial blood supply is likely to suffer late if at all, but obstruction of the lateral spinal artery at the foramen would tend to cause ischemia of the lateral region of the cord. The anterior spinal artery might conceivably be compressed by a midline protrusion, and in severe cervical spondylitis the vertebral artery and vein may undergo compression in their foramen.

Many writers, including Brain and associates,[4] Mair and Druckman,[6] and Clarke and Robinson,[2] have emphasized the role of vascular factors in spondylosis. Mair and Druckman[6] believed that the histologic changes in their patients were consistent with ischemia in the distribution of the anterior spinal artery and found that the blood vessels in the affected territory were thick walled due to fibrosis of the adventitia and, occasionally, surrounded by round cells. Girard, Garde, and Devic[7] also have described histologic changes in the spinal cord thought to be on a vascular basis but secondary to cervical spondylosis without compression of the cord. Bucy, Heimburger, and Oberhill[8] and Knight[5] have mentioned the anterior spinal artery as a possible etiologic point of interest. Bradshaw[1] reminds us that 2 or, at most, 3 unpaired radicular arteries supply the cervical cord and that foraminal compression of these vessels by osteophytes or adhesions associated with root-sleeve fibrosis may severely impair the blood supply of the cord. Frykholm[9] found that root-sleeve fibrosis is an actual problem in many cases of disk degeneration and osteophyte formation.

Another vascular change sometimes observed consists of apparently aberrant blood vessels coursing between the pia and arachnoid that often are associated with an arachnoiditis, which will be described later. These vessels seem to be small arteries and are seen best through the intact arachnoid when the subarachnoid space is distended with spinal fluid. With some degree of vascular insufficiency, a significant proportion of the blood supply of the cord may depend on these unusual blood vessels. The writer observed a patient with clinical and roentgeno- and myelographic evidence of spondylosis who, at operation, had the above-described vessels in the subarachnoid space in addition to a midline bony mass. Also, numerous adhesions were found at the lateral aspect of the cord and were dissected free. Possibly, the dissection disturbed these vessels and interfered with the blood supply of the cord; postoperatively, the patient had a severe quadriparesis that persisted and was much worse than before operation. The surgical implications are obvious and will be discussed later.

Bailey[10] has described the changes that occur in the spinal cord with aging. Thickening of the blood vessels increases with advancing age.

Payne and Spillane[11] and Hutchinson and Yates[12] have described vertebral artery compression by the osteophytes of cervical spondylosis.

CONNECTIVE TISSUE FACTORS

In addition to vascular changes that may take place in a state of chronic irritation or inflammation, connective tissue changes occur as a reaction to such states of longstanding disordered anatomy. These changes also may be involved in cervical spondylosis.

Taylor,[13] Brain and associates,[4] Bradshaw,[1] Clarke and Robinson,[2] and Russell[3] have described the adhesions that frequently are found at operation between the dura and arachnoid as well as the arachnoid and pia. This has been a common observation at this hospital and, usually, has been noted in conjunction with the vascular changes in the subarachnoid space mentioned earlier. This connective tissue change generally is referred to as an arachnoiditis but is a different process from that seen after infection and is more related to a chronic degenerative process. The myelograms of these patients may show a ragged and dif-

fuse area of nonfilling. The adhesions between the arachnoid and dura may, at times, make opening the dura without tearing the underlying arachnoid difficult.

Brain, Northfield, and Wilkinson[4] found that, in most cases, the dura is thickened and adherent to the posterior longitudinal ligament.

The role of the denticulate ligaments in the production of symptoms from cervical spondylosis has been well described by Kahn,[14] and most surgeons operating on patients with this disorder section the attachments of these ligaments to permit the cord to ride back over the anterior mass.

There is a decided individual difference in the size of the slip of tissue that attaches the denticulate ligament to the lateral wall of the spinal canal. In some individuals, this is a delicate, filamentous thread and, in others, is a coarse, fibrous band. Bedford, Bosanquet, and Russell[15] stated that microscopic sections from one of their patients showed thickened denticulate ligaments related to the area of cord degeneration. Possibly, the process causing the meningeal adhesions and root-sleeve fibrosis in these patients also involves the denticulate ligament as well, further complicating the situation. Existence of a coarse, fibrous attachment of the denticulate ligament, either fortuitous or reactive in origin, would seem to predispose a spondylotic individual to symptoms.

Frykholm[9] described the root-sleeve fibrosis seen with degenerative disk diseases excellently. He states that the dural sac becomes adherent to the osteophyte and initiates a reactive fibrosis in adjacent structures, involving not only the periradicular tissue but also the root sleeves.

O'Connell[3] pointed out the anatomic difference in the angle at which the nerve roots leave the spinal canal in the cervical region as compared to the remainder of the spine. The nerve roots pass anteriorly as well as laterally, and any fixation of the roots holds the cord anteriorly against the osteophyte. Brain, Northfield, and Wilkinson[4] found that the dura sometimes is attached to the intervertebral foramina and that, in all patients, the nerve roots are tethered by these adhesions, reducing the normal mobility of the cord and rendering it more susceptible to injury. Therefore, besides the tethering action of the denticulate ligament, a similar function may be attributable to the root sleeve.

MECHANICAL FACTORS

There is a considerable individual difference in the natural anteroposterior diameter of the cervical spinal canal. This first was demonstrated by Boijsen,[16] who measured the sagittal diameter of all of the cervical vertebrae of 200 healthy subjects on lateral roentgenograms. He found the minimum measurement at C4, C5, and C6 to be 14.2 mm.; the maximum, approximately 23 mm.; and the average, 18.5 mm. Wolf, Khilnani, and Malis,[17] using a fixed target distance of 72 in., found that the lower 5 cervical vertebrae had a sagittal diameter measuring 17 ± 5 mm. This measurement recently has been confirmed by Payne and Spillane.[11] Wolf, Khilnani, and Malis[17] emphasized that, in the cervical region, the sagittal diameter is the critical measurement because the lateral diameter far exceeds the sagittal.

This same measurement was made on lateral films of 15 of the patients in the present study with clinically significant cervical spondylosis; the average anteroposterior diameter was found to be 14.7 mm. If the distance between the most posterior extent of the osteophyte and the posterior wall of the canal is measured, the mean distance is 10.9 mm., which means that the canal is about 26% narrower at this site. This is a significant encroachment upon the spinal cord by the osteophyte, particularly if the patient normally has a narrow cervical spinal canal.

Payne and Spillane[11] found that, in spondylotic spines, the sagittal diameter was smaller than normal, especially (about 14 mm.) with paraplegia. Pallis, Jones, and Spillane[18] made similar observations. These findings suggest that patients with symptomatic cervical spondylosis tend to have sagittal diameters that are at the lower limits of normal. The inference is that this predisposes such patients to symptoms from a condition that would not disturb individuals with cervical canals of normal size.

Alexander, Davis, and Field[19] found that patients with hyperextension injuries of the spine also have sagittal diameters significantly less than the average measurement.

Fig. 1. Lateral view of cervical myelogram showing defects at the posterior aspect of the spinal canal at C3, C4, and C5

Another mechanical factor involves the ligamenta flava and the role they may play in causing cord compression, especially in hyperextension injuries. This aspect of the problem became apparent after studying a cervical myelogram of an elderly man who had a myelopathy of undetermined etiology. The only abnormal finding was in the lateral view (Fig. 1), which showed rather deep indentations at the posterior aspect of the spinal canal opposite the C3, C4, and C5 interspaces. The neck was in a moderate degree of hyperextension, and the indentations seemed to be due to the infolding of the ligamenta flava and of a sufficient degree to cause cord compression. It was then noted that this problem had been worked out on cadavers by Taylor.[20] He had studied myelograms of normal cadavers and found that, in hyperextension, there is marked encroachment upon the midcervical cord opposite the interspaces due to an infolding of the ligamenta flava. In a later article,[13] he stressed the importance of the ligamenta flava in relation to cervical spondylosis. Schneider, Cherry, and Pantek;[21] Clarke and Little;[22]

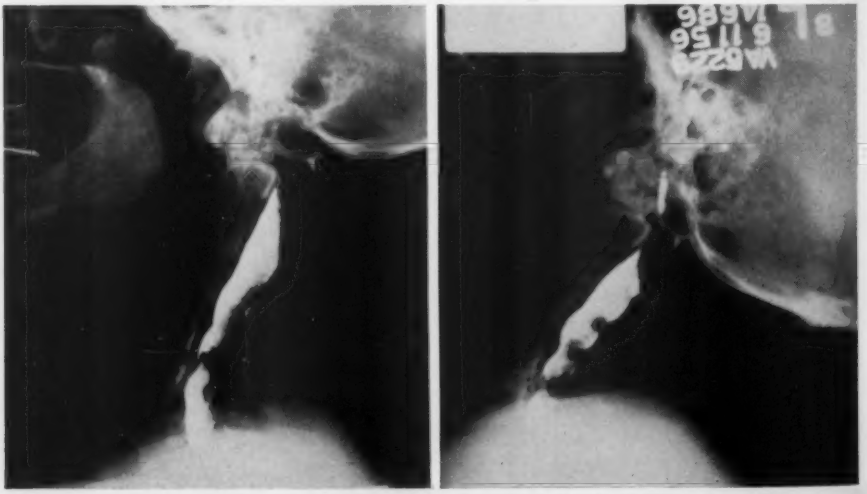


Fig. 2. Lateral views showing anterior and posterior defects at the C5 interspace and marked accentuation of the posterior defects in extension. This patient had onset of neck pain, which extended down the left arm to the wrist, after a fall from an upper bunk. Numbness in the arm and hand was accompanied by pain and numbness in the left leg. Extension of the head increased the pain and numbness.

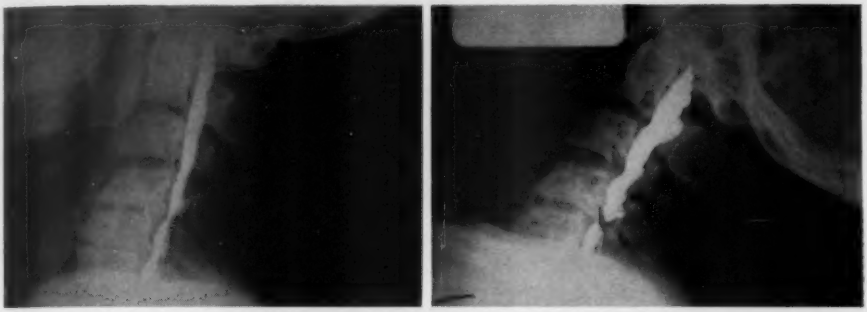


Fig. 3. Extension in this patient caused interruption of the Pantopaque column at the C4 and C5 interspaces. The sagittal diameter of the spinal canal is smaller than normal. This patient had had progressive spastic weakness in the legs; numbness, weakness, and clumsiness in the right hand; increased reflexes in the right arm; and bilateral extensor plantar responses for twelve years. A cystometrogram revealed a markedly hypertonic bladder.

Walker;[23] and Alexander, Davis, and Field[19] also have cited this.

Payne and Spillane[11] did anatomic dissections of the cervical spine and clearly showed on photographs that the ligamenta flava bulge anteriorly when the specimen is extended.

At this hospital, an attempt now is made to obtain a lateral view in flexion and moderate extension on myelograms of all patients suspected of having spondylosis or cervical myelopathy of undetermined etiology.

The myelographic column may be obliterated by the combination of anterior and posterior filling defects, and the total anteroposterior diameter of the canal may be severely compromised (Figs. 2, 3, and 4). The posterior defect often is particularly prominent at the site opposite the osteophytic spur at the anterior aspect of the spinal canal. Obviously, the effect of such space-taking lesions in producing symptoms would be greatly enhanced by a cervical spinal canal with an unusually narrow sagittal diameter.

Fig. 4. The posterior defects are maximum opposite the sites of the marked anterior spondylotic spurring. This man's grip and legs had been progressively weak for a year. There was occasional incontinence. Examination revealed hyperactive reflexes on the right and a right extensor plantar response. The right lower limb was slightly weak. Sensation to pin prick over the left lower leg and foot was decreased.

CLINICAL IMPLICATIONS OF THE LIGAMENTA FLAVA DEFECT

Acute trauma to an individual with a spondylotic cervical spine may damage the cord, even if the spondylosis had been asymptomatic before the trauma. Such trauma caused sudden neurologic deficit in 9 of Clarke and Robinson's[2] patients and in 8, 2 of whom died, of Brain, Northfield, and Wilkinson's[4] patients. In this series, 5 patients had similar histories, with the onset of severe quadriparesis or quadriplegia after trauma; 3 of these died after progressive deterioration, which followed the trauma.

Barnes[24] presented 15 cases of flexion injuries to the cervical spine and 6 cases of hyperextension injury. He found that all of the hyperextension injuries were in patients more

than 57 years of age and usually were associated with arthritis of the spine. All of the flexion injuries occurred in patients less than 50 years of age. The usual explanation for traumatic cervical cord injury in the absence of an acute ruptured disk or bony dislocation or fracture is sudden dislocation of the vertebrae, with immediate spontaneous realignment. Barnes[24] points out that this is untenable because hyperextension can cause cord compression only if it is sufficient to dislocate and lock at least 1 articular process. This presupposes a tearing of the ligamentous attachments, which, according to the evidence available, does not occur. The assumption that such locked facets would spontaneously reduce themselves also seems unrealistic. The infolded ligamenta flava, first described by Taylor,[20] offer a better explanation for this type of injury.

Payne and Spillane,[11] by anatomically dissecting the cervical spine, found that the mass at the anterior aspect of the spinal canal in spines with degenerative disease of the disk protruded even further into the canal when the spine was extended. This adds to the problem of hyperextension.

The hazards of such an injury can be understood readily when preexisting spondylosis is accompanied by vascular and connective tissue changes and, perhaps, a normally narrow spinal canal. This injury usually is one in which the individual falls forward on his face or is struck from behind.

Of the 6 patients with hyperextension injuries without fracture described by Barnes,[24] 5 died, as did the single patient presented by Berkin and Hirson.[25] These deaths, in addition to the 5 fatal injuries already cited, indicate that this is a serious disorder. The combination of a hyperextension injury of the neck resulting in a quadriparesis in an older individual with preexisting cervical spondylosis and no fracture is a warning to offer a guarded prognosis.

In answer to the question of why cervical spondylosis can present such a varied clinical picture, it probably can be said that this is related to the multiplicity of factors involved in each case and to the particular combination of these factors that may be playing the predominant role in any given case.

In patients whose involvement is primarily of the lateral columns, the role of the denticulate ligaments acting on these columns probably is the major offender, according to Kahn.[14] When the posterior columns are affected most, the ligamenta flava may be at fault primarily. If the patient has the syndrome of acute central cervical cord injury described by Schneider, Cherry, and Pantek,[21] which consists of disproportionately more motor impairment of the upper than of the lower extremities, bladder dysfunction, and varying degrees of sensory loss below the level of the lesion, the cord most likely has been compressed by 2 agents, anteriorly by the osteophyte and posteriorly by the ligamenta flava. If the neurologic deficit progresses, even after surgical decompression, the problem is primarily vascular, with either infarction or hematomyelia taking place.

Kaplan and Kennedy[26] described the effect of head posture on manometrics of the cerebrospinal fluid in cervical lesions. It was shown that a manometric block could be produced in extension that was not present in flexion. This test now is performed frequently and is known to be positive in patients with ruptured midline disks, cervical cord tumors, and cervical spondylosis.

Kaplan and Kennedy[26] have also stated that myelographic examination confirms the block in the extended position and that, after laminectomy and sectioning of the denticulate ligaments, the block disappears. They did not, however, offer an explanation for the block in extension only. Undoubtedly, the answer lies in the infolded ligamenta flava. This would explain why the test is nonspecific and positive in any condition in which space in the cervical canal is crowded.

ROENTGENOGRAPHIC IMPLICATIONS OF THE LIGAMENTA FLAVA DEFECT

In view of the individual difference in the anteroposterior diameter of the cervical spinal canal, this distance should be measured routinely when examining the plain films. If the measurement is unusually short and degenerative changes are associated, an early hint as to the process involved is provided.

As stated earlier, the roentgenographic and clinical findings are not correlated in cervical

Fig. 5. The midline defects at the C4 and C5 interspaces seen on the anteroposterior view are found, on the lateral view, to be primarily the result of the infolded ligamenta flava.

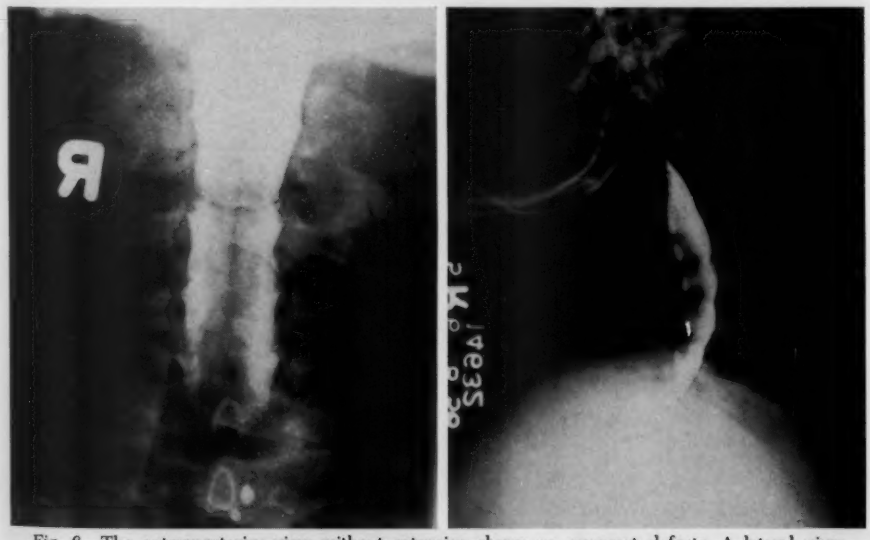


Fig. 6. The anteroposterior view without extension shows no apparent defects. A lateral view in extension reveals marked posterior indentations at C3 and C4.

spondylosis. Also, an inconstant correlation occurs between the plain roentgeno- and myelographic findings. Despite an advanced degree of spondylosis on roentgenograms, the myelogram may be normal, or the plain films may be normal and the myelogram may show, on the anteroposterior view, transverse ridges opposite the interspaces that are interpreted as the osteophytic masses of spondylosis. Interpretation of the transverse ridges that are thought to be characteristic of spondylosis is impossible without a lateral view of the neck in flexion and extension. The defect may not be due to spondylosis but to the infolded ligamenta flava (Fig. 5).

In unexplained cases of cervical cord disease, the lateral view in extension should be added to the myelographic examination (Fig. 6). The neck should not be markedly hyperextended during the myelographic examination or the cord may be damaged further. In many instances, an assistant must pull down on the arms to obtain a satisfactory lateral view of the lower cervical canal. The neck should not be hyperextended in patients with acute trauma and quadriplegia from spondylosis, and this may preclude myelographic examination altogether.

SURGICAL IMPLICATIONS OF THE LIGAMENTA FLAVA DEFECT

With the potential danger of hyperextension, the anesthetist should be forewarned of the situation and advised against hyperextension of the neck during endotracheal intubation of the anesthetized and relaxed patient. Symonds[27] mentioned probable cervical cord injuries in patients with spondylosis who were hyperextended during general anesthesia for tonsillectomy and dental extraction. Fender[28] cited 3 similar injuries probably related to hyperextension of the neck during endotracheal intubation for routine anesthesia.

If the ligamenta flava are as important in cervical spondylosis as implicated, laminectomy, with removal of these ligaments, would, in some cases, seem to be adequate treatment. This may well be the case in those instances in which, upon opening the dura and arachnoid, no evidence of anticipated cord compression is found and the tension on the denticulate ligaments is not impressive. In such a situation, the offending structure has been removed and the patient treated already.

This does not mean that opening the dura is not advocated, since one cannot distinguish patients in whom the cord is compressed against an anterior mass and in whom sectioning of the denticulate ligament relieves the situation from those who do not have this compression.

Laminectomy and sectioning of the denticulate ligaments probably should not be done in patients who have acute cord compression associated with spondylosis and hyperextension injuries of the spine without evidence of cervical fracture or fracture dislocation. The subarachnoid space usually is not blocked to manometric examination in such cases, and 3 of the patients with this disorder operated upon at this hospital died postoperatively.

Because of the frequent occurrence of numerous blood vessels in the subarachnoid space that may be adherent to the arachnoid and from which a portion of the blood supply of the cord is derived, great care must be taken to prevent tearing these vessels when opening the arachnoid preparatory to section of the denticulate ligaments. If extensive adhesions and vascular changes are apparent in the subarachnoid space, a hole should be made in the arachnoid of only a sufficient size to permit collapse of this space; then, the denticulate ligaments outside of the arachnoid in the subdural space are sectioned.

The rootlets emerging from the lower cervical cord pass inferiorly from their point of origin and are held close to the cord by the enveloping arachnoid. The rootlets then pass laterally and anteriorly to the foramen, carrying a sleeve of arachnoid with them. The cord may be relaxed markedly by first sectioning the denticulate ligaments and then cutting the fine arachnoid web at the inferior aspect or so-called axilla, of the nerve root. This is done bilaterally and is best accomplished with a pair of sharply pointed scissors. This area is usually devoid of blood vessels and, by thus releasing the arachnoid from around the roots, mobility of the cord is considerably increased. This overcomes the problem of the tethering action of the nerve roots and would seem to be more desirable than sectioning posterior roots, as suggested by O'Connell.[3]

SUMMARY

The problem of cervical spondylosis has been reviewed from many aspects, particularly that of pathogenesis. From the evidence available, this seems to be a complex situation in which numerous interrelated factors, many of which are fortuitous, are involved.

Whether symptoms arise from this chronic degenerative process of the cervical vertebrae and intervertebral disks depends upon the width of the sagittal diameter of the cervical spinal canal; physical size of the attachment of the denticulate ligaments; and presence of root-sleeve fibrosis, intradural adhesions, and associated vascular insufficiency of the cervical spinal cord.

The role of the ligamenta flava in compounding the disorder of the spinal canal is stressed, with special reference to hyperextension injuries of the cervical spine.

The work of Taylor[20] on cadavers is confirmed in living subjects.

The clinical, roentgenographic, and surgical implications of these problems are discussed and an attempt made to answer some of the questions raised by this interesting disease.

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REFERENCES

1. Bradshaw, P.: Some aspects of cervical spondylosis. Quart. J. Med. 26:177, 1957.
2. Clarke, E., and Robinson, P. K.: Cervical myelopathy: A complication of cervical spondylosis. Brain 79: 483, 1956.
3. Brain, R., Russell, W. R., Miller, H., and O'Connell, J. E. A.: Discussion on cervical spondylosis. Proc. Roy. Soc. Med. 49:197, 1956.
4. Brain, W. R., Northfield, D., and Wilkinson, M.: Neurological manifestations of cervical spondylosis. Brain 75:187, 1952.
5. Brain, W. R., Knight, G. C., and Bull, J. W. D.: Discussion on rupture of intervertebral disc in cervical region. Proc. Roy. Soc. Med. 41:509, 1948.
6. Mair, W. G. P., and Druckman, R.: Pathology of spinal cord lesions and their relation to clinical features in protrusion of cervical intervertebral discs. Brain 76:70, 1953.
7. Girard, P. F., Garde, A., and Devic, M.: Contribution à l'étude anatomique des manifestations médullaires observées au cours des discarthroses. Rev. neurol. 90:48, 1954.
8. Bucy, P. C., Heimburger, R. F., and Oberhill, H. R.: Compression of cervical spinal cord by herniated intervertebral discs. J. Neurosurg. 5:471, 1948.
9. Feykholm, R.: Cervical nerve root compression resulting from disc degeneration and root-sleeve fibrosis. Acta chir. scandinav. Supp. 160, 1951.
10. Bailey, A. A.: Changes with age in spinal cord. Arch. Neurol. & Psychiat. 70:299, 1953.
11. Payne, E. E., and Spillane, J. D.: The cervical spine: An anatomicopathological study of 70 specimens with particular reference to the problem of cervical spondylosis. Brain 80:571, 1957.
12. Hutchinson, E. C., and Yates, P. O.: The cervical portion of the vertebral artery: A clinicopathological study. Brain 79:319, 1956.
13. Taylor, A. R.: Mechanism and treatment of spinal-cord disorders associated with cervical spondylosis. Lancet 1:717, 1953.
14. Kahn, E. A.: Role of the dentate ligaments in spinal cord compression and the syndrome of lateral sclerosis. J. Neurosurg. 4:191, 1947.
15. Bedford, P. D., Bosanquet, F. D., and Russell, W. R.: Degeneration of spinal cord associated with cervical spondylosis. Lancet 2:55, 1952.
16. Boijsen, E.: Cervical spinal canal in intraspinal expansive processes. Acta radiol. 42:101, 1954.
17. Wolf, B. S., Khilnani, M., and Malis, L. I.: Sagittal diameter of the bony cervical spinal canal and its significance in cervical spondylosis. J. Mt. Sinai Hosp. New York 23:283, 1956.
18. Pallis, C., Jones, A. M., and Spillane, J. D.: Cervical spondylosis; incidence and implications. Brain 77:274, 1954.
19. Alexander, E., Davis, C. H., and Field, C. H.: Hyperextension injuries of the cervical spine. Arch. Neurol. & Psychiat. 79:146, 1958.
20. Taylor, A. R.: Mechanism of injury to spinal cord in neck without damage to vertebral column. J. Bone & Joint Surg. 33-B:543, 1951.
21. Schneider, R. C., Cherry, G. R., and Pantek, H.: Syndrome of acute central cervical spinal cord injury with special reference to mechanisms involved in hyperextension injuries of cervical spine. J. Neurosurg. 11:546, 1954.
22. Clarke, E., and Little, J. H.: Cervical myelopathy; a contribution to its pathogenesis. Neurology 5:861, 1955.
23. Walker, A. E.: Changing role of neurological surgery in medicine. J.A.M.A. 156:833, 1954.
24. Barnes, R.: Paraplegia in cervical spine injuries. J. Bone & Joint Surg. 30-B:234, 1948.
25. Berkin, C. R., and Hibson, C.: Hyperextension injury of neck with paraplegia. J. Bone & Joint Surg. 36-B:57, 1954.
26. Kaplan, L., and Kennedy, F.: Effect of head posture on manometrics of cerebrospinal fluid in cervical lesions: new diagnostic test. Brain 73:337, 1950.
27. Symonds, C.: Interrelation of trauma and cervical spondylosis in compression of cervical cord. Lancet 1:451, 1953.
28. Fender, F. A.: A new hazard in cervical laminectomy. J.A.M.A. 149:227, 1952.

Facial paralysis in poliomyelitis

Report of 3 patients with unusual delayed paralysis

Irving C. Sherman, M.D., and S. J. Kimelblot, M.D.

FACIAL PARALYSIS in poliomyelitis has been described in the earliest literature on the subject.[1] The incidence has varied from 5 to almost 50%,[2-6] depending on the specific epidemic, the attitude of the examiners, and the manner of determining the statistics. Occasionally, bilateral facial paralysis has been described.[5] Facial paralysis may be complete or incomplete as a result of the extent of involvement in the nucleus. We did not find any reference to facial paralysis of the supranuclear type from polioencephalitis, although such cases are not considered rare.

The occurrence of isolated facial paralysis in poliomyelitis has been the subject of considerable investigation. In 1932, de Lavergne, Abel, and Kissel[7] stated that facial paralysis may occur in association with spinal or bulbar involvement or as an isolated manifestation of the disease. They reported a surprisingly high number of 80 patients with isolated facial paralysis attributable to this infection. Smaller series of cases of isolated facial paralysis have been reported during typical outbreaks and are presumably due to the disease.[8-12] Some of these patients had spinal fluid pleocytosis.[13]

The usual criteria for attributing a case of facial paralysis to poliomyelitis were as follows: absence of other causes; presence of the same kind of general disturbance as was observed in patients suffering from paralysis of the limbs; and presence of an epidemic and seasonal incidence.[3,14,15] Many patients with facial paralysis were considered by these authors to have had poliomyelitis—even without spinal fluid examination or with normal spinal fluids.[4]

Little attention has been given to time that facial paralysis appeared. In general, onset was described as no different than the usual progression in this disease—the longest specific interval mentioned was four days.[4] General statements were made—such as that by Wernstedt[6] that the interval before the appearance of paralysis may be days or weeks, but no specific reference was made to paralysis of the face.

Our interest in these cases was stimulated by several unusual phenomena involving the facial nerve in patients with polimyelitis. We reviewed our data in relation to the problems discussed, but inadequately presented, in the literature and wish to record a study of 3 patients with unusual, delayed facial paralysis.

OBSERVATIONS

Incidence. The records of all the patients diagnosed as having poliomyelitis in Michael Reese Hospital, Chicago, during 1952-56 were reviewed (Table 1). Many patients came under personal observation.

Frequency. Of 407 patients with poliomyelitis, 267 had some form of paralysis. Of these, 203 patients had paralysis involving only spinal musculature; in 64, musculature supplied from the brain stem was involved. Some of these patients, of course, had bulbospinal distribution. Of the 64 patients with bulbar involvement, 34 had some type of facial involvement. Thus, approximately 50% of those patients with bulbar involvement had facial paralysis, while, of all 267 patients with paralysis, the face was involved in 12.7%. In 4 patients, facial paralysis was the only phenomenon of bulbar involvement, although these individuals also had evidence of spinal cord involvement elsewhere. The incidence of facial paralysis in all 407 patients diagnosed as having poliomyelitis—paralytic or nonparalytic—was 8.3%.

Table 1 demonstrates the great variation in incidence of bulbar cases in any one year, even though the proportion of paralytic to non-

From the Division of Neuropsychiatry, Michael Reese Hospital and Department of Psychiatry and Neurology, Chicago Medical School.

TABLE 1
INCIDENCE AND DISTRIBUTION OF PARALYSIS

	1952	1953	1954	1955	1956	*Total*
Total number with poliomyelitis	114	64	100	75	54	407
Nonparalytic cases	31	24	36	34	15	140
Paralytic cases	83	40	64	41	39	267
Number with any bulbar manifestation	27	8	17	11	1	64
Number with facial involvement	15	5	6	7	1	34
Isolated facial paralysis	0	1	0	0	0	1
Delayed facial paralysis	1	0	1	1	0	3

paralytic cases does not vary widely. It would suggest an obvious explanation for the great variability in frequency as reported from one epidemic to another.

Sex and age. Of the 20 males and 14 females, the youngest was 2 years old, the oldest 54 (Table 2). No statistical analysis was made of this distribution, but the age incidence certainly conforms to that usually noted with poliomyelitis in our area.

Side of involvement. In 15 patients, the facial involvement was entirely on the right side, in 18, on the left. The remaining patient had bilateral involvement.

Lower motor neuron vs. upper motor neuron lesion. A nuclear type of facial paralysis is usual in poliomyelitis. However, since the disease may be widespread and involve the cerebrum, a supranuclear facial paralysis may occur in conjunction with a hemiparesis of the upper motor neuron type. A careful review of our material did not produce any such cases. In all our cases, paralysis was considered to be nuclear. Surprisingly, in the review of the literature, we found no specific reference to an upper motor neuron lesion.

Isolated facial paralysis. A careful scrutiny of the phenomena of bulbar involvement was made in each patient. In 34 patients with facial paralysis, only 1 could be said to have an isolated facial paralysis—that is, no other evidence of bulbar or spinal involvement. Since the diagnoses were made by approximately 25 different physicians, this is of interest.

Case 1. A 5-year-old girl was admitted to Michael Reese Hospital on August 24, 1953, four days after the extraction of 2 infected molars under general anesthesia. At the time of extraction, the patient had a sore throat and vomited. The next afternoon, the child could not completely close the right eye, and the day before admission, the right face was completely paralyzed. On admission, she had a temperature of 103° F. rectally. The general physical examination was normal. The sockets of the extracted teeth were clear and without infection. No evidence of meningeal irritation was found. Head-drop and tripod signs were present, and, other than a complete right facial paralysis, there were no neurologic findings.

The spinal fluid contained 83 mg. per cent glucose, 21 mg. per cent protein, 65 mg. per cent chlorides, 4 red blood cells, and 42 white blood cells (32 polymorphonuclear leukocytes, 8 lymphocytes, 2 monocytes) per cubic millimeter. Pandy test was negative. The spinal fluid culture was negative. The remainder of the routine laboratory tests were normal.

The patient became afebrile after the second hospital day. She had mild spasm of the neck and back muscles without weakness. The facial paralysis was noticeably improved after three days. She was discharged, completely well, on the eleventh hospital day.

Time of appearance. Onset of facial paralysis is usually early. We found this true in our 34 patients who had facial paralysis with or without signs of other bulbar or spinal cord damage. The time of onset was consid-

TABLE 2
AGES OF 34 PATIENTS WITH FACIAL PARALYSIS

Age	*Number of patients*
0 to 10	20
10 to 20	6
20 to 30	4
30 to 40	3
40 to 50	0
50 to 60	1

TABLE 3
TIME OF ONSET OF FACIAL PARALYSIS

Day	*Number of patients*
0 to 1	25
0 to 2	4
0 to 4	1
0 to 5	1
10	2
11	1

ered in relationship to other paralytic phenomena (Table 3). If facial paralysis appeared within the first twenty-four hours of any paralysis, it was recorded as occurring in 0-1 day. In some patients, records did not reveal exact time of onset, but the patient may have come into the hospital on the second day of paralysis and, at that time, facial paralysis was noticed. Accordingly, paralysis was recorded as appearing in 0-2 days. One patient came into the hospital with facial paralysis on the fourth day and another on the fifth day, but date of onset was not known. From the table, it appears quite probable that the great majority of facial paralyses appeared early—certainly in the first twenty-four hours of paralysis anywhere. Of 3 patients in whom appearance was remarkably delayed, 1 developed bilateral paralysis eleven days after the first bulbar signs, and 2 developed unilateral paralysis ten days after the first bulbar signs. Because of the unusual features, these 3 patients are being described.

Case 2. A 32-year-old woman became ill on August 1, 1952, with fever and chills which subsided in forty-eight hours. However, the following day she had headache, fever, chills, and aching. On August 8, she had difficulty swallowing and noticed stiffness of the neck.

The patient was admitted to Michael Reese Hospital on August 9, 1952 with a temperature which ranged from 99 to 102.4° F. She had definite resistance of the neck to flexion, and a positive Brudzinski sign. No weakness or pathologic reflexes were found. Tendon and abdominal reflexes were brisk bilaterally. Sensation was intact. The patient had a positive head-drop sign and could not raise her head off the pillow. The right side of her palate moved slightly; the left side did not move at all. The clear, colorless spinal fluid contained 92 white blood cells (91% polymorphonuclear leukocytes and 9% monocytes) and 5 red blood cells per cubic millimeter; Pandy test, 3 plus; glucose, 61 mg. per cent; protein, 42 mg. per cent; and chlorides, 706 mg. per cent. The culture was sterile. The blood Kahn was negative, and blood count normal. Forty-eight hours after admission, the patient developed weakness of the left shoulder, involving the deltoid, abductor, and rotator muscles. She also had mild weakness of the biceps, triceps, pronators, and supinators of the arm. Wrist movements were normal. The left triceps reflex was absent, and the biceps was feeble. On August 13, she was afebrile.

On August 19, eleven days after the first manifestation of paralysis, the patient began to feel that her face was not moving. She had some weakness in her right forehead, and her right eye did not close as well as her left. The next day, complete, bilateral facial paralysis was found, and a fine nystagmus was present. No change occurred in the palatal movement. The clear, colorless spinal fluid was under a pressure of 110 mm. on August 22 and contained 1 red blood cell and 18 white blood cells per cubic millimeter (1 polymorphonuclear leukocyte and 17 lymphocytes); Pandy test, 3 plus; glucose, 64 mg. per cent; total protein, 138 mg. per cent; chlorides, 696 mg. per cent.

On August 25, six days after onset, facial recovery began. Just prior to the patient's discharge on September 10, completely normal, objective movements of her face occurred but it was a long time before she felt that her face was normal subjectively. A laryngeal examination showed that the left side of her soft palate and left pharyngeal wall were paralyzed or had questionable motion. The larynx was normal.

The patient recovered function of the palate almost a year later. At this time, she is normal.

Case 3. On August 28, 1954, a 52-year-old man began to have chills, fever, and night sweats. He had dysphagia three days later and regurgitated fluids through his nose. His voice became hoarse; laryngeal examination revealed paralysis of the left palate, diminished to absent pharyngeal reflex, and paralysis of the left vocal cord. No other evidence of neurologic deficit was found. On September 6, 1954, spinal puncture revealed clear, colorless fluid containing 68 mg. per cent total protein; 7 white blood cells per cubic millimeter (3 lymphocytes and 4 polymorphonuclear leukocytes); Pandy test was negative. A diagnosis of bulbar poliomyelitis was made.

He became afebrile on September 9, 1954. However, the next day—ten days after the first evidence of paralysis—he had complete paralysis of the muscles of the left side of the face. The patient was transferred to Michael Reese Hospital on September 10, 1954. The next day, his spinal fluid contained 1 lymphocyte per cubic millimeter with a total protein of 51 mg. per cent. The patient remained in the hospital until October 2, 1954, by which time his disability had greatly diminished. He recovered completely within a few weeks.

Case 4. The patient, a 29-year-old man, was admitted to Burnham City Hospital in Champaign, Ill., on October 7, 1955, with dysphagia and headache which had lasted twelve to twenty-four hours. His temperature was elevated. When he vomited, nasal regurgitation occurred. Spinal fluid on October 7 contained 5 white blood cells per cubic millimeter; Pandy test was 1 plus. In a repeat examination on October 8, 1955, spinal fluid contained 6 lymphocytes per cubic millimeter with a total protein of 68 mg. per cent. On October 14, he became afebrile, and, by this time, palatal weakness was static. Three days later—ten days after the first evidence of any paralysis—the patient noticed transient weakness in the left side of his face and numbness of his face and left upper lip. On October 18, he had difficulty using his mouth and lips.

On admission to Michael Reese Hospital on October 18, his general physical examination was entirely negative. The neurologic examination was normal except for severe weakness of all the muscles, including the platysma on the right side of his face. The palate hung down and to the right, rising on phonation to the left. The patient's speech was nasal; however, no fluid regurgitated in his nose, and swallowing was not difficult. Spinal fluid on October 19 was clear and sterile and contained 6 red blood cells and 25 white blood cells per cubic millimeter (24 lymphocytes and 1 polymorphonuclear leukocyte); total protein, 93 mg. per cent; glucose, 50 mg. per cent; chlorides, 690 mg. per cent; Pandy test was negative. The blood Kahn and spinal fluid Wassermann were negative.

The patient's condition remained static until his discharge on October 29, 1955. Spinal fluid at that time contained 162 mg. per cent total protein, but, unfortunately, cell count was not done.

The patient was examined again on December 10, 1955; he had no subjective or objective evidence of facial weakness. Palatal weakness on the left was much less severe, but some nasal tone remained.

DISCUSSION

Because of the lack of a specific diagnostic test for poliomyelitis, many paralytic phenomena occur during epidemic periods which are mistakenly diagnosed as poliomyelitis—various types of acute infectious polyneuritis, including the Guillain-Barré syndrome, spinal cord tumors, progressive muscular atrophy, and so on. The natural course of these diseases soon makes the correct diagnosis apparent. However, with such an entity as Bell's palsy, nothing unusual may occur to distinguish the disease from paralysis due to poliomyelitis.

The literature contains numerous reports of isolated facial paralysis as a sign of poliomyelitis—incidence occasionally rising as high as 60% of those patients in whom the face was involved.[3] All authors have been faced with the question of what criteria will distinguish poliomyelitis from Bell's palsy. Most have accepted the criteria of seasonal incidence, presence of an epidemic, generalized signs of infection, and, perhaps, pleocytosis in spinal fluid.

In our 34 patients with facial paralysis in poliomyelitis, only 1 case was considered in this category. The child had generalized signs of infection, evidence of meningeal irritation clinically, and an increase of cells in the spinal fluid. All other patients had some other evidence of paralytic phenomena—nasal speech, difficulty in swallowing, ocular palsy, or extremity involvement. Of the 34, 4 had only facial paralysis as a bulbar sign, along with some paralysis of the extremities.

We were able to find only 2 authentic efforts to prove the etiologic relationship of poliomyelitis to facial paralysis; the first by Levaditi[16] in 1910 when he induced facial paralysis in monkeys by injecting the virus; the other in 1936 by Toomey,[17] who suggested from his experiments that the virus could find its way to the seventh nerve nucelus via the chorda tympani and the superior olivary nucleus.

In 1955, Unger[18] concluded from his work that idiopathic Bell's palsy was a manifestation of poliomyelitis. His studies are poorly controlled and not adequate evidence that poliomyelitis is the cause of Bell's palsy. Nor do these studies warrant his conclusion that poliomyelitis should be removed from the epidemic class and labeled endemic.

Since 1 of the criteria for the diagnosis of poliomyelitis is the presence of increased cells and protein in the spinal fluid, we became curious about changes in the spinal fluid in cases diagnosed as Bell's palsy by presumably competent observers. We were not able to find many direct references to this subject. Merritt and Fremont-Smith[19] mentioned that the spinal fluid was entirely normal in 6 patients with a peripheral facial paralysis (Bell's palsy). In a study of 500 patients with idiopathic facial paralysis, Park and Watkins[20] reported the spinal fluid findings in 24 patients.

Of these, 10 had an elevation of protein, and 3 had pleocytosis of 12, 20, and 47 cells per cubic millimeter.

We can vouch for the infrequency of spinal fluid examinations in patients with Bell's palsy. In the private practice of one of us, 60 such patients were seen in the last ten years.

Only 6 of these patients had their spinal fluid examined. All were adults; 2 had an identical amount of protein, 72 mg. per cent; one, protein content of 102 mg. per cent; and 1 a cell count of 9 lymphocytes and protein of 30 mg. per cent eight days after onset of the paralysis.

Although some of these patients were seen in the late fall and early winter, none were considered to have poliomyelitis. How would one classify them if they were seen during a poliomyelitis epidemic? It is our opinion that occasionally—at least in Bell's palsy—the spinal fluid may show increased protein and pleocytosis but that this in itself does not warrant placing the patient in a different diagnostic category.

In our opinion, isolated facial paralysis is a rare entity in poliomyelitis, and, before such a diagnosis is accepted, undoubted clinical signs of generalized infection, meningeal reaction, and spinal fluid pleocytosis should be found. Seasonal incidence is not sufficient to warrant diagnosis of poliomyelitis. In our series of 60 patients with Bell's palsy seen during the last ten years, the disease occurred evenly throughout the year.

Time of onset of facial paralysis in patients with bulbar poliomyelitis generally appears to be quite early in the course of the disease. We were not always able to determine the exact time of onset of facial paralysis from the recorded history except occasionally to note the time when it was first mentioned.

In 25 patients, facial paralysis was definitely recorded either as the first finding or as following within twenty-four hours any evidence of paralysis elsewhere; 4 patients had facial paralysis by the second day, 1 by the fourth day, and 1 by the fifth day. Probably, if records were more detailed, these few patients noted on the second and fifth day would have been seen earlier.

We encountered 3 patients with unusual, delayed appearance of facial paralysis not clearly mentioned in the literature with which we were familiar.

One was a female with bulbospinal disease who developed bilateral facial paralysis eleven days after the palatal weakness appeared and six days after she had become afebrile. At that time, she still had 18 cells per cubic millimeter and 138 mg. per cent protein in her spinal fluid.

The second was a male who developed a left facial paralysis ten days after the appearance of weakness of the left palate, vocal cord, and pharynx, and one day after he had become afebrile. His spinal fluid was normal at this time.

The third patient was a young man who had right palatal weakness and, ten days later (3 days after becoming afebrile), paralysis of the left side of his face. At this time, he had 25 cells per cubic millimeter in his spinal fluid.

All 3 of these patients recovered completely from signs of palatal, pharyngeal, and facial weakness.

Logically, facial paralysis should be related to the other signs of bulbar involvement etiologically, even though specific proof for the relationship is lacking. Only 2 of the patients still had evidence of inflammatory reaction in the spinal fluid, but such changes may or may not be present in bulbar syndromes due to poliomyelitis. Prognosis in bulbar poliomyelitis should be cautious when progression apparently has stopped. One cannot be sure for at least eleven days after the first appearance of paralysis.

CONCLUSIONS

1] Of 267 patients with paralytic poliomyelitis, only 64 had some evidence of facial or bulbar paralysis.

2] Of 64 patients with bulbar poliomyelitis, 34 had some involvement of the facial nerve. Incidence of facial paralysis in all 267 paralytic patients was 12.7%.

3] An isolated facial paralysis in poliomyelitis occurred in 1 of 34 patients; 4 patients had facial paralysis as the only bulbar sign, but they also had some paralysis of the extremities.

4] Facial paralysis is not uncommon during poliomyelitis epidemics and may be accompanied by an increase in cells and protein in the

spinal fluid. In the absence of other bulbar phenomena, paralysis of the extremities, signs of generalized infection, or meningeal reaction, a diagnosis of Bell's palsy is justified.

5] Facial paralysis in poliomyelitis nearly always appeared within one day of the appearance of paralysis in the bulb or elsewhere.

6] Descriptions were given of 3 patients in whom unusual delay in appearance of facial paralysis occurred; 1 was bilateral delayed for eleven days, and 2 were unilateral delayed for ten days.

REFERENCES

1. Fishbein, M. E., Salmonsen, E. M., and Hektoen, L.: Bibliography of Infantile Paralysis, 2d ed., J. B. Lippincott & Co., Philadelphia, 1951.
2. Bernstein, H. G. G., Clark, J. M. P., and Turnbridge, R. E.: Acute anterior poliomyelitis among service personnel in Malta. Brit. M. J. 1:763, 1945.
3. Aguis, T., Bartolo, A. E., Coleiro, C., and Seddon, H. G.: Clinical features of poliomyelitis epidemic in Malta 1942-1943. Brit. M. J. 1:759, 1945.
4. Rascoff, H.: Prognosis of facial nerve paralysis in poliomyelitis. J. Pediat. 35:567, 1949.
5. Moore, E. W.: Fate of the face in poliomyelitis. Lancet 1:1092, 1952.
6. Wernstedt: Ergebnisse der innern Medizin und Kinderheilkunde. XXV, 1924. As quoted by Wilson in *Neurology*, Williams & Wilkins Co., Baltimore, 1940, p. 229.
7. de Lavergne, V., Abel, E., and Kissel, P.: Paralysie faciale et poliomyélite. Paris méd. 1:488, 1932.
8. Alberca Lorente, R.: Formas abortivas de poliomyelitis epidémica. Arch. de neurobiol. 13:315, 1933.
9. Gentile, A.: Unusual forms of poliomyelitis. Reforma med. 49:900, 1933.
10. Marque, A. M.: Algunas breves consideraciones sobre las ultimas 363 observaciones de la enfermedad de Heine-Medin. Semana méd. 1:1219,1936.
11. Velasco, B. L.: Facial paralysis in Heine-Medin disease: cases studied during Buenos Aires epidemic in 1936. Arch. am. de Méd. 12:54, 1936.
12. Kissel, P.: Epidémic de paralysies faciales d'origine poliomyelitique. Rev. neurol. 69:725, 1938.
13. Chalier, J., Planchu, M., and Badinaud, L.: Sur deux cas de paralysies faciales d'allure épidémique et d'origine poliomyélitique probable. Lyon méd. 153: 714, 1934.
14. Stapleton, T.: Facial palsy and poliomyelitis. Lancet 2:510, 1949.
15. Krischek, J.: Facialislähmung und Poliomyelitis. Arztl. Wchnschr. 5:421, 1950.
16. Levaditi. Compt. rend. Socl. de Biol. 68:264, 1910.
17. Toomey, J. A.: Seventh nerve as a possible pathway for the transmission of the virus of poliomyelitis. Am. J. Dis. Child. 51:58, 1936.
18. Unger, M.: Bell's palsy and poliomyelitis. Eye, Ear, Nose & Throat Month. 34:501, 1955.
19. Merritt, H. H., and Fremont-Smith, F.: The Cerebrospinal Fluid. W. B. Saunders Co., Philadelphia, 1938.
20. Park, H. W., and Watkins, A. L.: Facial paralysis; analysis of 500 cases. Arch. Phys. Med. 30:749, 1949.

Hyperinsulinism: rare cause of epilepsy

Donald W. Mulder, M.D., and Joseph G. Rushton, M.D.

HYPERINSULINISM is a rare clinical syndrome which frequently masquerades as an epileptic disorder but rarely causes true epileptic seizures.

Breidahl and associates[1] reported that patients with functioning adenomas of the islet cells of the pancreas frequently are diagnosed as epileptic. Of 91 patients seen at the Mayo Clinic, 37 had what were called convulsive seizures as a clinical symptom.

Epileptic seizures are common symptoms. The recognition of seizures secondary to hyperinsulinism is of clinical importance, as hyperinsulinism due to a pancreatic adenoma may be cured surgically.[2] Because of the frequent confusion in diagnosis between hyperinsulinism and epilepsy, some authors have suggested that every patient with seizures should have a fasting blood sugar determination. In our experience and that of others,[1,2] the routine determination of fasting blood sugar has not proved to be an economic or effective aid in the recognition of hyperinsulinism.

In order to differentiate epilepsy due to hyperinsulinism from epilepsy due to other causes, we reviewed the records of the 91 patients with hyperinsulinism previously described by Breidahl and associates.[1]

The term, hyperinsulinism, as used here, is reserved for those patients in whom a hyperfunctioning tumor of the islets of Langerhans has been found. An epileptic seizure as defined for this and other studies means a brief, abrupt, recurrent, paroxysmal, stereotyped cerebral storm inappropriate to the immediate situation and followed by transient impairment of cerebral function.[5]

In the 91 patients, transient recurrent cerebral symptoms and signs were common. The symptoms of these patients were carefully analyzed, and the criteria just mentioned for recognition of an epileptic seizure were applied to these symptoms.

Usually, cerebral symptoms and signs were not abrupt in onset or brief in duration nor were they particularly stereotyped. Thus they did not meet our criteria for epileptic seizures. Attacks most commonly began with a mild, hardly noticeable nervousness, apprehension, and hunger, eventually terminating in confusion, unconsciousness, convulsions, coma, and, perhaps, death. The symptoms might subside spontaneously, but, in most instances, symptoms were terminated by eating.

Breidahl and associates[1] reported that 37 of these 91 patients had convulsive seizures. Our review of these symptoms suggested that in many instances these patients did not have epilepsy as we have defined it. Of these patients, 21 described the recurrent cerebral symptoms as gradual in onset, variable in manifestations, and of long (several hours to days) duration. The character of these attacks was distinctly different from an epileptic seizure.

We concluded that only 16 of the 91 patients had had epileptic seizures. Of the patients with epileptic seizures, 15 had seizures best classified as generalized convulsions. In some, the attack was typically grand mal, while in others, loss of consciousness occurred with only mild tonic or clonic movements. In 9 patients, prodromal symptoms of paresthesia, dazed feeling, sweating, pallor, faintness, hunger, or diplopia occurred, usually thirty minutes or more before onset of a convulsion.

In 14 of 16 patients, the first seizure occurred between the ages of 31 and 63 years. In 2, the first seizure occurred at ages 9 and 23 years, respectively. Frequency of these seizures varied greatly. In 8 patients, attacks occurred several times a week to several times a month; 1 patient had suffered only 4 con-

From the Section of Neurology, Mayo Clinic and Foundation, Rochester, Minn.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

vulsions; 2 patients had 2 convulsions each; 5 patients had single seizures, and 1 of these had a single convulsion while undergoing a fast which was part of a diagnostic study to determine the presence or absence of hyperinsulinism.

In 3 patients, a generalized seizure was the first recognized indication of illness. In addition to convulsions, each of these 3 patients subsequently suffered from other symptoms of hypoglycemia. In 11 patients, the first seizure occurred one to three years after the first symptoms attributable to hypoglycemia. In 2 patients, the first convulsion developed fifteen and twenty-one years after the first symptoms of hypoglycemia.

Neurologic examination and electroencephalographic study conducted at a time when the patient did not have hypoglycemia usually produced normal results. The exceptions are few; 1 patient had a positive Babinski sign and an abnormal increase in the activity of muscle stretch reflexes on the left side. In only 3 patients were electroencephalographic abnormalities noted: slight dysrhythmia in 2 and bitemporal slow waves in 1.

In these 16 patients with epilepsy, the cause of hyperinsulinism was adenoma of the islet cells of the pancreas in 9 and adenocarcinoma in 7. We could discover no relationship between the type of pancreatic lesions and the character or frequency of the epileptic seizures.

COMMENT

Hyperinsulinism and epilepsy are both clinically characterized by episodic, cerebral disturbances. In hyperinsulinism, the episodic disturbances are rarely true epileptic seizures. More frequently, the cerebral symptoms may masquerade as a convulsive disorder. Some patients with hyperinsulinism do have seizures secondary to the hyperinsulinism. Of the 91 patients included in this study, epileptic seizures were the first manifestation of hyperinsulinism in only 3. In the other 13 patients with seizures, the epileptic symptoms occurred late in the course of illness and did not present a diagnostic problem. Thus, in this group of 91 patients with hyperinsulinism, seizures were rarely the initial symptom and were never the only, or even the principal, symptom.

If patients receiving therapeutic insulin are excluded, hyperinsulinism is a rare condition. In 1954, at the Mayo Clinic,[6] 1,284 patients were diagnosed as having convulsive disorders. In the same year, the diagnosis of hyperinsulinism as defined here was given to only 3 patients, and the diagnosis of epilepsy was not considerd for any of the 3. Our impression is that the incidence of hyperinsulinism as a cause of seizures is even less than the 0.1% mentioned by Merritt.[3]

Although hyperinsulinism is a rare cause of epilepsy, those recurrent cerebral symptoms of hyperinsulinism which masquerade as epilepsy are of concern to the physician. These symptoms are gradual in onset, persist for hours to days, and are variable in their expression. Because of the infrequency of the hyperinsulin syndrome, the clinician may not consider this possibility when he sees the patient with periodic and bizarre cerebral symptoms. In his search for a diagnosis, he frequently considers the symptoms to be unusual epileptic manifestations or hysterical fugues. The diagnosis of hyperinsulinism in most instances is overlooked because the clinician has not considered the condition as a possibility. The patient with hyperinsulinism—or members of his family—is usually aware of the relationship of hunger to the onset of attacks and the prompt relief of symptoms by ingesting food.

The diagnosis can be suspected in most instances on the basis of the patient's description of spells and can be confirmed by (1) precipitating an attack by fasting up to seventy-two hours, (2) obtaining low levels of blood sugar during an attack, and (3) relieving symptoms by administration of glucose.[1]

REFERENCES

1. Breidahl, H. D., Priestley, J. T., and Rynearson, E. H.: Clinical aspects of hyperinsulinism. J.A.M.A. 160:198, 1956.
2. Howard, J. M., Moss, N. H., and Rhoads, J. E.: Hyperinsulinism and islet cell tumors of pancreas with 398 recorded tumors. Internat. Abstr. Surg. 90:417, 1950.
3. Merritt, H. H.: Textbook of Neurology. Philadelphia, Lea & Febiger, 1955.
4. Wechsler, I. S.: Textbook of Clinical Neurology. Philadelphia, W. B. Saunders, 1958.
5. Sections of Neurology and Section of Physiology, Mayo Clinic and Foundation: Clinical Examinations in Neurology. Philadelphia, W. B. Saunders, 1956.
6. Mulder, D. M., Yoss, R. E., Daly, D., Rushton, J. G., and Dodge, H. W., Jr.: Symposium on clinical significance of epileptic seizures. Proc. Staff Meet. Mayo Clin. 33:467, 1958.

Reevaluation of lumbar puncture

A study of 129 patients with papilledema or intracranial hypertension

Julius Korein, M.D., Humberto Cravioto, M.D., and Mario Leicach, M.D.

THIS STUDY REEVALUATES lumbar puncture in diseases causing intracranial hypertension. Although many believe that lumbar puncture is contraindicated in patients with increased intracranial pressure and/or papilledema, the information obtained from the cerebrospinal fluid is often of great importance in diagnosis as well as in management of the patient.

The immediate problem facing the physician presented with a patient who has signs and symptoms of intracranial hypertension is to perform specific diagnostic tests. Although diagnosis of intracranial tumor may be evident, many patients have other conditions which are nonneoplastic and cause intracranial hypertension and papilledema.[1–5]

Lumbar puncture is a simple procedure and often aids in differentiation of these diseases. Whenever feasible, lumbar puncture should precede more involved surgical procedures, for instance, ventriculography. After lumbar puncture, the next diagnostic procedure to be performed is more clearly evaluated. However, the degree of danger of lumbar puncture to the patient with intracranial hypertension is a question that must be adequately answered beforehand. The danger of the alternative diagnostic procedure—such as ventriculography—must then be considered. Finally, the choice must depend on the relative dangers of the procedures under consideration and the diagnostic information obtainable from each.

Cushing, Dandy, and others[6–10] have stated categorically that lumbar puncture should never be done in the presence of increased intracranial pressure and especially in the presence of papilledema. The major contention of many of these authors is that sudden death caused by herniation of the brain stem and the cerebellar tonsils into the foramen magnum may occur upon removal of cerebrospinal fluid via the lumbar route.

However, one must examine these principles in terms of their historical background. In early use, lumbar puncture was not limited to diagnostic studies but was considered a major therapeutic procedure to reduce increased intracranial pressure.[11] Needles of large bore (sizes 16 to 12) were used during this period, and large quantities of cerebrospinal fluid were removed. Up to 1915, Schoenbeck[12] had reported 71 deaths related to lumbar puncture; half were in patients with brain tumor. From 1915 until the review of the literature by Freemont-Smith and Putnam in 1932, only 4 additional deaths were uncovered.[13]

We wish to emphasize that the method of lumbar puncture in this study involves gradual removal of small quantities of cerebrospinal fluid for diagnostic purposes only, rather than rapid removal of large quantities of fluid for the purposes of medical decompression.[10,14]

Authors such as Merritt, Ayer, DeJong, and others[8,13,15–17] have said that the rule of not performing lumbar puncture in patients with increased intracranial pressure is not absolute. Even in the earlier literature, Levinson,[18] Masson,[19] and Schaller[20] reported that careful lumbar puncture could be performed safely in patients with intracranial hypertension. Some of these authors stated that lumbar puncture might be more hazardous in patients with subtentorial tumors but thought that most complications were caused by abuse and care-

From the Department of Neurology, Third Division, New York University–Bellevue Medical Center.

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lessness during the procedure. Masserman and Schaller[21] and Masserman[22] conducted a series of experimental studies which supported their views that sudden herniation of the brain rarely occurred. The impression that herniation of the brain stem was a gradual process is shared by other clinicians.[8]

Thus, we see that the present study and the more recent studies of the past few years are not without precedent and represent an attempt of investigators to gather valid data which will clarify the controversial problem of the dangers and value of lumbar puncture in patients with intracranial hypertension.

METHODS AND CRITERIA

On the Third Neurological Division of New York University–Bellevue Medical Center, careful lumbar puncture was performed in all patients with papilledema or signs of increased intracranial pressure. In most patients, a No. 20 spinal needle was used. All patients lay in the lateral recumbent position. The present data are a combination of the authors' personal experiences during 1954-57 and cases which could be compiled from available records since 1950.

The patients were divided into 2 groups for comparative study. The first group was 70 patients with unequivocal papilledema graded from 1+ to 3+. Early papilledema was 1+ and consisted of definite blurring and slight elevation of the disk margin with congestion of the veins. Severe papilledema—in which changes were more evident and retinal hemorrhages occurred—was graded 3+. An intermediate state was 2+. The subjectivity of this classification is recognized, but, in almost all cases, description agreed after repeated observation by more than one observer.

The second group was 59 patients without papilledema but in whom the initial pressure on lumbar puncture was reliably increased above 240 mm. of water. These values were considered valid only when the patient was relaxed and lying on his side and when sufficient time was given for the manometer reading to reach a stable level. In those cases taken from the charts, such careful control could not be insured but reliability of the pressure values could be checked by other symptoms of increased intracranial pressure and by repeated lumbar puncture and findings at operation.

All patients with papilledema or increased cerebrospinal fluid pressure had lumbar puncture before any surgical procedure,* and no patient with an available chart who fulfilled these criteria was excluded.

The criterion used for *possible* complications of lumbar puncture was any unfavorable change within forty-eight hours after the procedure, regardless of the opinion as to the cause.† We emphasize that these changes have a temporal, but not necessarily causal, relationship to lumbar puncture. These stringent criteria for possible complications were selected so that no causally related complication would be overlooked; later each case could be judged individually by the authors as well as by the reader.

OBSERVATIONS AND RESULTS

As can be seen in table 1, 51.4% of the 70 patients with papilledema had neoplasms, 17.1% had intracranial hemorrhage, 5.7% had infections, 12.9% had subdural and intracerebral hematomas, 8.6% had encephalopathies of various types, and 4.3% had miscellaneous diseases, including serous meningitis. The mean cerebrospinal fluid pressure indicates that usually papilledema reflects increased intracranial pressure, although this was not true in all patients, since approximately 15% with papilledema did not have cerebrospinal fluid pressure above 200 mm. of water.

Of 36 patients with tumor and papilledema, 5 had tumors in the posterior fossa. No unfavorable changes occurred in any of these patients within forty-eight hours after diagnostic lumbar puncture.

Of 12 patients with intracranial hemorrhage and papilledema, 1 had an unfavorable change after lumbar puncture.

The patient was a 41-year-old woman who had had a craniotomy for removal of a right frontoparietal hemangioma more than one year prior to admission. She entered the hospital with a skull fracture and intermittent seizures and was comatose. Examination soon

*Two patients did have a craniotomy more than a year before present lumbar puncture.

†Headaches were not considered a complication in this study.

after admission revealed a 3+ bilateral papilledema with hemorrhages. Lumbar puncture revealed an initial pressure of 310 mm. with bloody, xanthochromic fluid. The patient went into respiratory arrest five minutes after lumbar puncture. She was given intracardiac caffeine and artificial respiration and resumed breathing but died fifteen hours after admission. No postmortem examination was performed.

In the remainder of the 22 patients with papilledema, no possible complications of lumbar puncture were seen.

The diagnoses of the 59 patients without papilledema but with increased cerebrospinal fluid pressure are presented in table 2. Only 25% of these patients had neoplasms. An increase in the number of patients with intracranial hemorrhages and the addition of cases with cerebrovascular thrombosis are evident. In this group, 7 had *possible* complications which occurred within forty-eight hours after lumbar puncture.

Of 15 patients with tumor, 3 had tumors in the posterior fossa. In this group, 2 patients had possible complications.

The first patient was a 58-year-old woman who entered the hospital in a lethargic state but who was easily aroused. History and findings indicated an expanding cerebral lesion. Lumbar puncture showed initial pressure of 270 mm. The patient did well during the first twenty-four hours after lumbar puncture, but, within the next twenty-four hours, she became more lethargic. A craniotomy was performed which revealed an extensive frontal lobe glioblastoma. The patient died twenty-six hours after craniotomy. No autopsy was performed.

The other patient was a 46-year-old man who was admitted to the hospital with carcinoma of the lung. He had no papilledema, but, because of signs of intracranial disease, lumbar puncture, revealing initial pressure of 330 mm., was performed. The patient became lethargic in twenty-four hours but recovered spontaneously. Later, a ventriculogram was performed. Tumor of the third ventricle was diagnosed, and the patient died one month later.

Of 16 patients with intracranial hemorrhage, 10 had hypertension and vascular disease. Possible complications occurred in 2.

The first patient was a 55-year-old man with hypertension who was admitted to the hospital with sudden onset of coma and right hemiplegia. His blood pressure was 230/115. On admission, lumbar puncture revealed an initial pressure of over 500 mm. and bloody xanthochromic fluid. The patient died three and one-half hours after admission. No autopsy was performed.

The second was a 67-year-old comatose woman with intracranial hemorrhage presumably related to hypertension. A lumbar puncture showed initial pressure of over 600 mm. and grossly bloody, xanthochromic fluid. The patient's coma deepened, and she died within twenty-four hours. No autopsy was performed.

Of the remaining 28 patients with increased cerebrospinal fluid pressure, 3 had *possible* complications.

A 60-year-old man with subdural hematoma and previous alcoholism and head trauma was admitted with signs of a slight organic mental syndrome. Lumbar puncture revealed an initial pressure of 300 mm. with clear, colorless, cerebrospinal fluid. He became lethargic twenty-four hours after lumbar puncture, and bur holes were made. Bilateral subdural hematomas were evacuated. The patient improved and was discharged from the hospital twenty days after admission.

The remaining 2 patients in whom changes occurred after lumbar puncture are included in the miscellaneous group.

A 48-year-old man had had myocardial infarction, cerebrovascular accident, and severe diabetes. He entered the emergency ward in stupor, went into shock, and had acute congestive heart failure because of another myocardial infarction. The patient's head and eyes persistently turned to the left, and, after poor response to treatment of congestive heart failure and shock, lumbar puncture was performed. The pressure was over 600 mm.; the cerebrospinal fluid was otherwise normal. The patient died within three hours after admission. No autopsy was performed.

The last patient was a 32-year-old Negro woman with previous active tuberculosis who was admitted to the psychiatric ward because of mental changes and confusion. The positive physical and neurologic findings included signs of pulmonary involvement and an organic men-

tal syndrome. Laboratory findings included a hemoglobin of 6.5 gm. and a leukocytosis of 18,000 with a shift to the left. Chest roentgenograms showed massive infiltration of the right upper lobe. The patient had a generalized seizure with focal onset on the left two days after admission. After the seizure, she remained in coma with bilateral Babinski reflex and fixed, dilated pupils. Some nuchal rigidity was present. Lumbar puncture showed initial pressure of 560 mm. and clear, colorless cerebrospinal fluid without cells. Protein was 165 mg. per cent.

Antituberculous therapy was initiated, but the patient's condition remained unchanged. Lumbar puncture was repeated six hours later. Initial pressure was 450 mm., and pink fluid was found in all 4 tubes with no supernatant xanthochromia. The patient died approximately eighteen hours after the seizure and two hours after the last lumbar puncture. Autopsy showed tuberculosis of the right upper lobe with bronchiectasis and severe fibrotic pulmonary involvement. The brain was grossly normal except for congestion of the cerebral veins and a small amount of blood in the subarachnoid space over the pons. No tonsillar herniation was seen. Sections of the cerebrum and brain stem were normal. Microscopic sections showed an occasional perivascular hemorrhage and no inflammation. The final impression was that death was caused by anoxia resulting from anemia and pulmonary disorder. The cause of the seizure and the microscopic hemorrhages was not determined, and the cause of death was not considered to be primarily cerebral in origin.

DISCUSSION

Possible complications. If all unfavorable changes after lumbar puncture are considered complications causally related to the procedure, incidence of 11.9% in the group without papilledema is more significant than incidence of 1.4% in the group with papilledema. To determine whether unfavorable changes were actually caused by lumbar puncture is difficult; the circumstances of each individual patient must be assessed.

The single *possible* complication which occurred in the patients with papilledema was in a patient with intracranial hemorrhage from skull fracture and hemangioma. The cessation of respiration after the lumbar puncture may be related to the procedure, but the condition of this patient was so critical prior to lumbar puncture that we hesitate to definitely implicate the procedure. In the authors' experience, occasionally just moving a patient with severe intracranial hemorrhage has caused temporary cessation of respiration. The death rate in the condition itself is certainly high enough. Furthermore, the patient had a craniotomy one year prior to lumbar puncture. Although sufficient doubt is present, we will assume, for comparative purposes, that this is a complication of lumbar puncture.

In the group with increased cerebrospinal fluid pressure but without papilledema, the death of the patient with acute myocardial infarction, acute congestive heart failure, diabetes, and previous episodes of myocardial and cerebral infarction was probably not an actual complication of lumbar puncture. In the 2 patients with intracranial hemorrhage, the progressive, rapidly deteriorating course was probably not adversely affected by the spinal tap, especially in view of the incidence of death in such patients. In the patient who had bilateral subdural hematomas, the usual fluctuating course must be considered and the lethargy that followed the lumbar puncture cannot be definitely ascribed to the procedure.

The transient lethargy in the patient with the third ventricle tumor and the lethargy in the patient with the frontal lobe glioma may have been causally related to lumbar puncture. However, these changes cannot definitely be attributed to the procedure. Many patients with similar lesions who had no lumbar puncture often show similar unfavorable changes.

The dramatic case of the patient with tuberculosis and seizures who died after lumbar puncture would seem to be an instance in which lumbar puncture contributed to deterioration. However, postmortem findings showed no herniation of the brain stem and no convincing evidence that lumbar puncture contributed to the patient's death.

The relationship to lumbar puncture of these 8 possible complications is at best equivocal. A definite causal relationship is difficult to ascertain between lumbar puncture and the

TABLE 1
CASES WITH PAPILLEDEMA

Diagnosis	*Number*	*Per cent*	*Mean pressure in mm. H_2O*	*Possible complications after LP*
Neoplasm	36	51.4	300	0
Intracranial hemorrhage	12	17.1	340	1
Subdural and intracerebral hematoma	9	12.9	350	0
Encephalopathies	6	8.6	230	0
Infection	4	5.7	195	0
Miscellaneous	3	4.3	265	0
Total	70	100.0	300	1

subsequent changes in a patient's condition. From this study, one can conclude that *actual* complications occur far less than *possible* complications and that incidence of complications is no greater in patients with papilledema than in patients with increased cerebrospinal fluid pressure without papilledema.

Value in diagnosis and management. In the group of patients with papilledema, over 45% had nonneoplastic lesions (Table 1). Patients were observed with intracranial hemorrhages, encephalitis, central nervous system syphilis, serous meningitis, and other encephalopathies in which diagnosis was established with the aid of lumbar puncture.

A 30-year-old woman entered the psychiatric service in a confused, apathetic state. After several days, she gradually became lethargic. At that time, examination revealed no focal neurologic signs and no nuchal rigidity: 2+ bilateral papilledema was present. Lumbar puncture showed bloody xanthochromic cerebrospinal fluid, and, at a later date, an aneurysm was found. In patients such as these, the diagnostic value of lumbar puncture prevented the performance of unnecessary ventriculography.

In patients with intracranial tumors and papilledema, lumbar puncture was not detrimental and aided in establishing diagnosis. When indicated, further diagnostic and surgical procedures were promptly undertaken. After lumbar puncture in patients in whom neoplasm seemed evident, findings led the investigators to consider tumor a less likely possibility. Accordingly, management of the patient was altered, and procedures such as pneumoencephalography were used for con-

TABLE 2
CASES WITHOUT PAPILLEDEMA BUT INCREASED CEREBROSPINAL FLUID PRESSURE

Diagnosis	*Number*	*Per cent*	*Mean pressure in mm. H_2O*	*Possible complications after LP*
Neoplasm	15	25.4	320	2
Intracranial hemorrhage	16	27.1	310	2
Subdural and intracerebral hematoma	10	17.0	375	1
Encephalopathies	8	13.6	300	0
Thrombosis	6	10.2	275	0
Infection	2	3.4	260	0
Miscellaneous	2	3.4	575	2
Total	59	100.1	325	7

TABLE 3
LUMBAR PUNCTURE IN CASES WITH PAPILLEDEMA

Author	Nature of study	Cases with lumbar puncture and papilledema	Causes of Papilledema			Possible complications
			Neoplasms	Posterior fossa	Nonneoplastic	
Masson, 1927	LP in 200 cases of presumed brain tumor	144	144	(42)	0†	1
Schaller, 1933	LP in 103 cases with increased intracranial pressure	49	37	(?)	12	2
Hepburn, 1938	LP in 25 cases with papilledema	25	17	(3)	8	0
Lubic and Marotta, 1954	LP in 401 cases of verified brain tumor	46(79*)	46(79*)	(12)(17*)	0†	1
Sencer, 1956	LP in 87 cases with papilledema	56	38	10	18	0
Erman, 1957	LP in 108 consecutive cases of verified brain tumors	28	28	(1)	0†	0
Present series	LP in 129 cases with increased cerebrospinal fluid pressure or papilledema	70	36	(5)	34	1
Total	1,053 cases reviewed	418(79*)	346	(73)	72	5(1.2%)

*Questionable papilledema
†Only neoplasms studied

firmation. The displacement method of pneumoencephalography was used in which no cerebrospinal fluid is removed.[23]

A 26-year-old woman who had had a severe headache ever since tooth extraction fifteen days before entered the hospital. She was vomiting and had hazy vision. On physical examination, she had 3+ bilateral papilledema with hemorrhages. No other abnormalities were seen. A lumbar puncture revealed an opening pressure of 280 mm. and a total protein of 23 mg. per cent. A diagnosis of serous meningitis was considered. Her vision worsened in the following week. A pneumoencephalogram using the displacement technic was performed with no untoward effects. The entire ventricular system was normal. The patient, treated with ACTH and daily therapeutic lumbar punctures, had cerebrospinal fluid pressure ranging from 80 to 380 mm. Two weeks after admission, her vision had considerably improved and the papilledema had disappeared completely. A repeat pneumoencephalogram prior to discharge was normal. Follow-up finds the patient in good health and with normal vision. In this patient, as well as in others with nonneoplastic disease, lumbar puncture was important not only in diagnosis but in total management.

REVIEW OF THE LITERATURE

In the literature, many of the previously reported complications were not due to diagnostic lumbar puncture where only a few cubic centimeters of cerebrospinal fluid were slowly removed but to therapeutic lumbar puncture where large quantities of cerebrospinal fluid were rapidly removed in attempted medical decompression. To gain information about relative incidence of complications, large series of cases were carefully analyzed in which lumbar puncture was performed in the presence of papilledema. Single case reports are not adequate to measure incidence of complications. The series reviewed include a significant number of cases with papilledema in which lumbar puncture was performed and are summarized in table 3. In other series, patients with neoplasms, papilledema, or increased cerebrospinal fluid pressure had lumbar puncture as a diagnostic study, but, in these reports, the discussion is directed toward other problems or insufficient data are given.[1,24,25]

In table 3, the data from the present series and from 6 others are presented.

Mason[19] reviewed 200 consecutive cases with signs and symptoms of increased intracranial pressure due to brain tumor in which lumbar puncture was performed. Papilledema

was present in 144 of these patients: all were presumed to have brain tumor; in 42, tumor was suspected in the posterior fossa. Presence of a tumor was verified in 67. In this series, a *possible* complication occurred in a patient with a suspected neoplasm who died twenty-two hours after lumbar puncture. Because of the patient's condition prior to the procedure, the author questions the causal relationship between the spinal tap and the patient's death.

In his series, Schaller[20] reviewed 103 cases in which lumbar puncture was done in the presence of signs and symptoms of increased intracranial pressure. Of the 103 patients, 49 had papilledema and 37 had verified neoplasms. Of those patients with papilledema, 2 children with cerebral neoplasms died. One 4½-year-old child died thirteen and one-half hours after lumbar puncture. Necropsy revealed rupture of a vascular carcinoma of the thalamus; the brain stem and cerebellum were normal.

The second child, an 8-year-old with bilateral papilledema who had cyanosis and cardiac complications prior to lumbar puncture, died six hours after the procedure. He had a cystic tumor in the right parietal region; the base of the brain was normal. The author points out that cerebellar herniation and brain stem compression did not occur in either of these 2 children.

In 1938, Hepburn[26] reviewed 25 cases with papilledema in which lumbar puncture was performed prior to operation. Of 17 patients with neoplasms, 3 had tumors in the posterior fossa. Nonneoplastic disease, such as encephalitis, was found in 8. No deaths occurred within forty-eight hours after the procedure, and the author did not believe that lumbar puncture affected these cases adversely.

Lubic and Marotta[27] reviewed 401 cases of verified brain tumor in which lumbar puncture was performed prior to any surgical procedure. Of these, 46 had unequivocal papilledema and 79 had equivocal papilledema. Of the 46 with unequivocal papilledema, 12 had tumors in the posterior fossa. Of this entire series of 401 cases, 1 possible complication is reported in a case with papilledema.

A 62-year-old woman with bilateral papilledema had headache, became stuporous, and developed focal neurologic signs twelve hours after lumbar puncture. A ventriculogram was performed which revealed a right temporal lobe mass lesion; the patient died forty-eight hours after ventriculography. A glioblastoma was found at biopsy.

Sencer's series[28] reviewed 87 consecutive cases which had papilledema from all causes. Of these, 56 cases had lumbar puncture prior to surgical procedure. Neoplasm was present in 38, of which 10 tumors were in the posterior fossa. Papilledema was due to nonneoplastic disease in 18 cases. No lumbar puncture complications were observed.

In an unpublished study, Erman[29] reviewed 108 consecutive verified brain tumors; 1 of the tumors was in the posterior fossa. Of these, 28 had papilledema, and lumbar puncture was performed prior to any surgical procedure. No deaths or complications related to the procedure were observed.

In our present study of 129 patients, 70 with papilledema had lumbar puncture. In 36, neoplasm was the cause of papilledema; 5 of the tumors were in the posterior fossa. In 34 patients, papilledema was related to nonneoplastic disease. One *possible* complication has been described.

The cause of papilledema in these patients was usually neoplasm, but since 3 of these studies were restricted only to neoplasms, incidence of papilledema caused by tumor is not accurately reflected in the statistics. If the series that review only neoplasms are eliminated, then 72 out of 200 had papilledema due to nonneoplastic disease.

Of 1,053 cases with neoplasms, increased intracranial pressure, or papilledema, 418 had lumbar puncture performed in the presence of papilledema; 1.2% had *possible* complications. In the present series, complications occurred in 1.4%. This is the percentage of *possible* complications, since complications are not necessarily caused by lumbar puncture. The incidence of death due to lumbar puncture in the presence of papilledema must be well below 1.2%. None of these possible complications occurred in any of the 73 patients with posterior fossa tumors and papilledema (see table 3). Certainly, the incidence of complications was no greater in subtentorial neoplasms.

When considering the advisability of lumbar puncture in a patient with papilledema,

the statistical findings presented above should be weighed against the possible complications of ventriculography[30–33] and other alternative procedures and the diagnostic and therapeutic value to the specific patient.

CONCLUSIONS

Lumbar puncture was performed in 70 patients with papilledema and 59 patients with increased cerebrospinal fluid pressure without papilledma. The incidence of *possible* complications—any unfavorable changes within forty-eight hours—was significantly higher in the group without papilledema. Complications that did occur were probably not caused by lumbar puncture. From this study and a review of similar studies from the literature, one can say that the actual complications of careful diagnostic lumbar puncture in the presence of papilledema are much less than 1.2%.

Use of careful lumbar puncture in the diagnosis and management of patients with papilledema is of definite value and may prevent unnecessary ventriculography or surgery. Therefore, the authors conclude that papilledema and increased intracranial pressure are not absolute contraindications to careful, diagnostic lumbar puncture. Lumbar puncture should be performed to aid in diagnosis or management of the patients with papilledema or increased intracranial pressure.

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REFERENCES

1. Berg, L., Rosomoff, H., Aronson, N., Silberman, M., and Pool, J. L.: Syndrome of increased intracranial pressure without localizing signs. Arch. Neurol. & Psychiat. 74:498, 1955.
2. Meredith, J. M.: Elimination of nonsurgical lesions in brain tumor suspects. South. M. J. 41:31, 1948.
3. Grant, F. C.: Differential diagnosis of tumor of brain; importance of considering renal hypertension with choked disk. Arch. Neurol. & Psychiat. 27:816, 1932.
4. Fremont-Smith, F.: Cerebrospinal fluid in differential diagnosis of brain tumor. Arch. Neurol. & Psychiat. 27:691, 1932.
5. Baker, A. B.: Clinical Neurology. New York City, Paul B. Hoeber, 1955.
6. Cushing, H.: Surgery of the Head. From Surgery, Its Principles and Practice. W. W. Keen, ed., Philadelphia, W. B. Saunders, 1908, pp. 17-276.
7. Cushing, H.: Some aspects of pathological physiology of intracranial tumors. Boston Med. & Surg. J. 141: 71, 1909.
8. Nash, C. S.: Cerebellar herniation as a cause of death. Ann. Otol., Rhin. & Laryng. 46:673, 1937.
9. Walker, A. E.: Intracranial Tumors. From Textbook of Medicine, 8th ed. Cecil and Loeb, Philadelphia, W. B. Saunders, 1951, pp. 1470-1478.
10. Verbrugghen, A.: Spinal puncture. S. Clin. North America 26:78, 1946.
11. Quincke, H.: Lumbar Puncture from Diseases of Nervous System, Modern Clinical Medicine. A. Church, New York City, D. Appleton, 1907, pp. 223-258.
12. Schoenbeck, quoted by Schaller.[20]
13. Fremont-Smith, F., and Putnam, T. J.: Value of lumbar puncture in diagnosis of suspected brain tumor. J. Nerv. & Ment. Dis. 76:261, 1932.
14. Korein, J., Feigin, I., and Shapiro, M. F.: Oligodendrogliomatosis with intracranial hypertension. Neurology 7:589, 1957.
15. Merritt, H. H.: Cerebrospinal fluid in cases of tumors of brain. Arch. Neurol. & Psychiat. 34:1175, 1935.
16. DeJong, R. N.: Neurologic Examination, New York City, Paul B. Hoeber, 1952. pp. 961-989.
17. Ayer, J. B.: Cerebrospinal fluid (lumbar) in brain tumor; analysis of 67 cases of tumors and cysts of brain. J.A.M.A. 90:1521, 1928.
18. Levinson, A.: Cerebrospinal Fluid in Health and Disease. St. Louis, C. V. Mosby, 1923, pp. 60-134.
19. Masson, C. B.: The dangers of diagnostic lumbar puncture in increased intracranial pressure due to brain tumor, with a review of 200 cases in which lumbar puncture was done. Research Nerv. & Ment. Dis. Proc. 8:422, 1927.
20. Schaller, W. F.: Propriety of diagnostic lumbar puncture in intracranial hypertension. J. Neurol. & Psychopath. 14:116, 1933.
21. Masserman, J. H., and Schaller, W. F.: Intracranial hydrodynamics, experiments on human cadavers. Arch. Neurol. & Psychiat. 29:1222, 1933.
22. Masserman, J. H.: Cerebrospinal hydrodynamics. Arch. Neurol. & Psychiat. 32:523, 1934.
23. Cravioto, H., Korein, J., and Villanova, J.: Pneumoencephalography with minimal withdrawal of cerebrospinal fluid. Confinia neurol. 17:213, 1957.
24. Comfort, M. W.: Yellow spinal fluid associated with tumor of brain. Arch. Neurol. & Psychiat. 15:751, 1926.
25. Puusepp, quoted by Merritt.[15]
26. Hepburn, H. H.: Risk of spinal puncture. The Canad. M. A. J. 39:449, 1938.
27. Lubic, L. G., and Marotta, J. T.: Brain tumor and lumbar puncture. Arch. Neurol. & Psychiat. 72:568, 1954.
28. Sencer, W.: Lumbar puncture in presence of papilledema. J. Mt. Sinai Hosp. New York 23:808, 1956.
29. Erman, S. L.: Consideration of lumbar puncture in diagnosis of brain tumor. Unpublished data. Cornell University, 1957.
30. Grant, F. C.: Ventriculography and encephalography. Arch. Neurol. & Psychiat. 27:1310, 1932.
31. Dekaban, A. S.: Is needle puncture of brain entirely harmless? Neurology 8:556, 1958.
32. David, M., Ruggiero, G., and Talairach, J.: Comparison between encephalography and ventriculography. Acta radiol. 42:37, 1954.
33. Norlen, G., and Wickbom, I.: Relative merits of encephalography and ventriculography for investigation of intracranial tumors. J. Neurol., Neurosurg. & Psychiat. 21:1, 1958.

CASE REPORT

Angioinvasive nonchromaffin paraganglioma of the glomus jugulare

Shankunny Shreekumar, M.B.,* and Paul R. Rosenbluth, M.D.

THE DISCOVERY by Guild[8] of a hitherto unknown structure in the temporal bone—which he named glomus jugulare — removed much of the obscurity from the origin and classification of tumors of the middle ear. Guild described a collection of tissue, similar to the carotid and aortic bodies, located in the adventitia of the bulb of the jugular vein close to the floor of the middle ear, or along the tympanic branch of the glossopharyngeal nerve. The histologic pattern was found to be identical with that of the carotid body, as was the blood supply and innervation.

De Castro[5,6] and Le Compte[11] suggested that the carotid body might be a chemoreceptor and stated that "the functions of the glomus jugulare, paraganglion ciliare and cells associated with the ganglion nodosum of the vagus are unknown, but in view of their resemblance to the carotid and aortic bodies in morphology and innervation, it is perhaps justifiable to classify them also as chemoreceptors."[11]

After Guild's discovery, Rosenwasser[12] made the first report of a tumor of the middle ear with a histologic pattern suggesting a paraganglioma of the carotid body type. Subsequently, similar tumors have been reported, including 33 cases collected by Siekert[15] from the Mayo Clinic and a review of 90 cases by Bickerstaff and Howell.[3]

Of the cases reported in the literature, 8 glomus jugulare tumors showed gross evidence of vascular invasion without distant metastasis (see table).[1-4,7,9,14] Only 3 cases of histologically proved distant metastasis are recorded in the literature.[10,13,16]

This article presents an additional report of an angioinvasive, nonchromaffin paraganglioma arising from the right glomus jugulare with invasion of the right sigmoid sinus and jugular vein, destruction of the petrous portion of the temporal bone, and intracranial extension.

CASE REPORT

A 68-year-old woman who had been in generally good health was admitted to Mount Sinai Hospital. She had had severe pain in the right side of the head and face for three months. The pain was constant and increased when she lay down so that she found it necessary to sit up in bed all night. A month before admission, the patient entered another hospital for treatment of a swollen gland in the right side of the neck. Operation revealed a pulsating expansile mass interpreted by the surgeon as an aneurysm of the external carotid. The mass had since grown into a throbbing lump. In addition, the patient had difficulty in talking, had to eat slowly, and could swallow only with difficulty. She had lost her appetite, had experienced progressive weakness over the months preceding admission, and had noticed recent weight loss. The patient was known to be hypertensive and had shortness of breath on exertion and tachycardia. Cholecystectomy was performed when she was 26, tonsillectomy when she was 60, and a "cyst of the womb" was removed in 1956. Her parents had died of old age; 1 sister had died of a heart attack.

Physical Examination. Pulse was 112 per minute, temperature, 101.4° F., blood pressure, 150/80. The patient was an elderly

From the departments of Pathology and Neurosurgery, Mount Sinai Hospital, Chicago.
*Present address: Georgetown University Hospital, Washington, D. C.

ANGIOINVASIVE GLOMUS JUGULARE TUMORS

No.	Author	Age	Sex	Duration of symptoms	Vessel invaded	Involvement of temporal bone	Intracranial extension
1	Bennett	53	F	5 years	Sigmoid, transverse and petrosal sinuses	Yes	Yes
2	Berg	44	M	4 years	Jugular vein	Yes	No
3	Bickerstaff	66	F	42 years	Jugular vein, sigmoid, petrosal and cavernous sinuses	Yes	Yes
4	Birrel(1)	55	F	—	Jugular vein, transverse sinus	Yes	Yes
5	Birrel(2)	42	M	5 years	Jugular vein, transverse sinus	Yes	Yes
6	Eggston	56	F	2 years	Sigmoid sinus	Yes	No
7	Henson	63	F	4 years	Jugular vein, sigmoid sinus	Yes	Yes
8	Seiffert	?	F	5 years	Jugular vein, sigmoid sinus	Not reported	Not reported
9	Shreekumar	68	F	3 months	Jugular vein, sigmoid sinus	Yes	Yes

white female, cooperative, but lethargic and somnolent. She answered questions in a whisper with some stridor. Her pupils were equal and reacted sluggishly to light. She was unable to look to the extreme right with the right eye and was unable to close the right lid. Fundus examination revealed blurring of the right disk margin. She had right peripheral facial paresis, severe venous engorgement of the right side of the neck, a pulsating mass extending from the mastoid prominence to the base of the neck, and an overlying transverse operative scar. No bruit was heard over the neck mass which seemed to transmit pulsation from the carotid artery but apparently did not pulsate itself. Internal carotid artery pulsation was readily felt in the posterior pharynx. Lymph nodes were not palpable. The right side of the soft palate was paralyzed. The hypopharynx and larynx were normal except for bulging of the right lateral pharyngeal wall because of the mass lying under the sternocleidomastoid muscle. The right ear drum was intact, but an irregular bulge of the drum with several dark red nodules on its surface was noted. The tympanic membrane pulsated. The neck mass was aspirated and venous blood obtained. Roentgenograms of the skull showed extensive erosion of the right petrous bone (Fig. 1).

The clinical impression was: tumor of base of skull invading the middle ear and petrous bone and extending into the neck obstructing the jugular vein. Involvement of the recurrent laryngeal and facial nerve was felt to be due to extension of the tumor into the neck and temporal bone. The findings seemed to suggest a glomus jugulare tumor.

The patient died from terminal pneumonitis forty-eight hours after admission.

Fig. 1. Skull roentgenogram showing destruction of medial right petrosal ridge

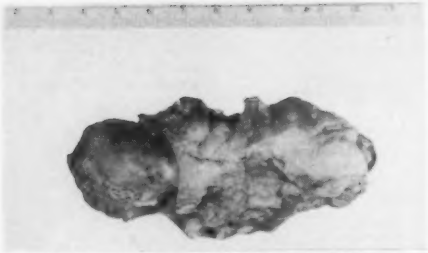


Fig. 2. Segment of the right jugular vein distended by tumor thrombus which produced a palpable mass

Fig. 3. Base of brain showing tumor in the right cerebellopontine angle

Fig. 4. Sections through hind brain showing compression of brain stem and cerebellum by tumor

Autopsy Findings. An autopsy was performed three hours after death. Examination of the right side of the neck revealed a slightly elevated, oval mass extending from just below and posterior to the angle of the mandible to midway down the neck and measuring 5.5 x 3 cm. This was a well-circumscribed mass which did not appear to be attached to the skin or subcutaneous tissues. No abnormal lymphadenopathy was palpable. Incision of the skin of the neck revealed the mass to consist of a 6-cm. segment of the internal jugular vein which was enormously distended due to the presence within the lumen of a firm, rubbery, fusiform mass of brownish-gray tissue with a smooth, glistening surface measuring 9 x 3.5 x 3 cm. (Fig. 2). In close proximity and lying between the mass and the larynx was a fluctuant, oval mass containing pus. Cultures from this cavity grew a gram-positive diphtheroid. Superior to this pocket and near the right lateral aspect of the pharynx, the tissues were firm and thickened. The trachea was in the midline, and the mediastinum was not displaced.

Removal of the calvarium revealed a normal dura. The right sigmoid sinus had, within its lumen and patchily adherent to its wall, small masses of light brown, rubbery tissue similar to that seen in the jugular vein. Inspection of the base of the brain showed a raised, spherical mass of purplish-red tissue in the right cerebellopontine angle compressing the medial half of the inferior surface of the right lobe of the cerebellum and medulla oblongata. This mass measured 4 x 3 x 2 cm. The external surface was irregular and comprised of tumor nodules (Fig. 3).

Inspection of the base of the skull showed that the tumor had begun in the temporal bone and eroded its petrous portion. Coursing around the tumor from below could be seen the right sixth nerve which appeared compressed in its proximal third. Coronal sections through the hind brain showed that the tumor mass in the right cerebellopontine angle compressed the brain stem and the cerebellum (Fig. 4).

Microscopic Examination. The tumor was composed of nests of cells arranged in an alveolar pattern supported by a well vascularized fibrous stroma (Fig. 5A). The cells

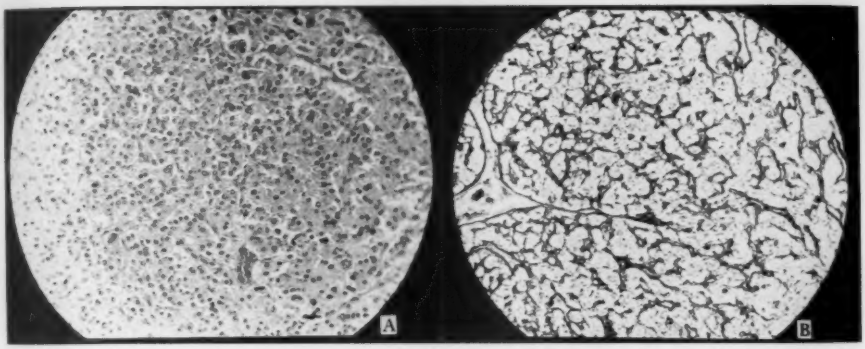


Fig. 5. (*A*) Microscopic section of tumor. Nests of tumor cells arranged in an alveolar pattern supported by a well vascularized fibrous stroma (Hematoxylin-eosin × 215). (*B*) Characteristic pattern with nests of tumor cells, surrounded by reticulin fibers (Silver impregnation for reticulin. Snook × 90)

were uniformly large with round or ovoid vesicular nuclei and pale eosinophilic cytoplasm. Although mitotic figures were not visualized, some of the nuclei appeared irregular, hyperchromatic, and pyknotic. Reticulin stains showed the nests of tumor cells to be surrounded by fine reticulin fibers. These fibers, however, did not surround individual cells (Fig. 5*B*). Sections through the mass in the right jugular vein revealed a picture essentially similar to that seen in the tumor from the cranial cavity. Microscopic examination of the petrous portion of the temporal bone showed replacement of normal elements of the marrow by nests of tumor cells lying in a fibrous stroma (Fig. 6). The pattern was similar to that seen in the tumor of the cranial cavity. Sections through the right sigmoid sinus showed small fragments of tissue adherent to the wall. These consisted of nests of tumor cells lying in a well vascularized stroma. Chromaffin stains were negative.

Study of the rest of the organs, including the cervical lymph nodes and liver, showed no evidence of metastasis.

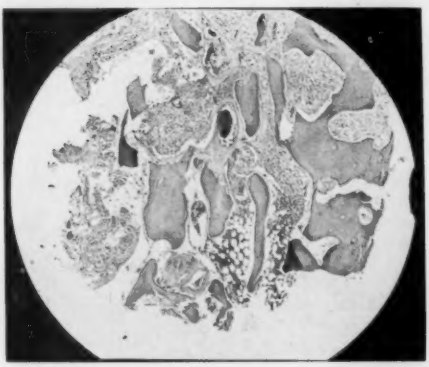


Fig. 6. Microscopic sections through right temporal bone. The normal elements of the marrow have been completely replaced by tumor cells except for a small area. (Hematoxylin-eosin × 30)

SUMMARY

A patient who had nonchromaffin paraganglioma arising in the right glomus jugulare is described:

A clinical diagnosis of glomus jugulare tumor was made, and autopsy revealed a neoplasm with microscopic characteristics of a nonchromaffin paraganglioma with invasion of the right sigmoid sinus, extension to the right internal jugular vein, infiltration and destruction of the petrous portion of the temporal bone, and intracranial extension with compression of the brain stem. No evidence of metastasis to other organs was found.

A review of the literature reveals 11 patients in whom direct or circumstantial evidence of angioinvasiveness was seen: 8 had gross and/or microscopic evidence of vascular invasion; 3 had distant metastasis.

REFERENCES

1. Bennet, M., Zurhein, G. M., and Bast, T. H.: Glomus jugulare tumor with intracranial extension. Arch. Otolaryng. 66:257, 1957.
2. Berg, N. O.: Tumours arising from the tympanic gland (glomus jugularis) and their differential diagnosis. Acta path. et microbiol. scandinav. 27:194, 1950.
3. Bickerstaff, E. R., and Howell, J. S.: Neurological importance of tumours of glomus jugulare. Brain 76: 576, 1953.
4. Birrell, J. H. W.: The jugular body and its tumour. Australian & New Zealand J. Surg. 24:195, 1955.
5. de Castro, F.: Sur la structure et l'innervation de la glande intercarotidienne (glomus caroticum) de l'homme et des mammiferes et sur un nouveau systeme d'innervation autonome du nerf glossopharyngien. Trav. du lab. d. recherches biol. de l'Univ. de Madrid 24:365, 1926. (Abstract: LeCompte, P. M., Atlas of Tumor Pathology, Sect. IV, Fasc. 16, p. 9, Tumors of the Carotid Body and Related Structures (Chemoreceptor system), National Research Council, Washington, D. C., 1951).
6. de Castro, F.: Sur la structure et l'innervation du sinus carotidien de l'homme et des mammiferes. Nouveaux faits sur l'innervation et la fonction du glomus caroticum. Trav. du lab. d. recherches biol. de l'Univ. de Madrid 25:331, 1927-8. (Abstract: See ref. 5).
7. Eggston, A. A., and Wolff, Dorothy: Histopathology of Ear, Nose and Throat. Williams and Wilkins Company, Baltimore, 1947, p. 478.
8. Guild, S. R.: A hitherto unrecognized structure, the glomus jugularis in man. Anat. Rec. 79 (suppl. 2): 28, 1941.
9. Henson, R. A., Crawford, J. V., and Cavanagh, J. B.: Tumours of the glomus jugulare. J. Neurol., Neurosurg. & Psychiat. 16:127, 1953.
10. Lattes, R., and Waltner, J. G.: Nonchromaffin paraganglioma of the middle ear (carotid body-like tumor; glomus-jugulare tumor). Cancer 2:447, 1949.
11. Le Compte, P. M.: Atlas of Tumor Pathology, Sect. 4, Fasc. 16, Tumors of the Carotid Body and Related Structures (Chemoreceptor system). National Research Council, Washington, D. C., 1951, p. 9.
12. Rosenwasser, H.: Carotid body tumor of the middle ear and mastoid. Arch. Otolaryng. 41:64, 1945.
13. Rosenwasser, H.: Metastases from glomus jugulare tumors. Arch. Otolaryng. 67:197, 1958.
14. Seiffert, A.: Endotheliom des Mittelohres kompliziert durch Sinus-thrombose. Ztschr. f. Hals-, Nasen- u. Ohrenh. 35:348, 1934.
15. Siekert, R. G.: Neurologic manifestations of tumors of the glomus jugulare, chemodectoma, nonchromaffin paraganglioma or carotid body-like tumor. Arch. Neurol. & Psychiat. 76:1, 1956.
16. Winship, T., Klopp, C. T., and Jenkins, W. H.: Glomus-jugularis tumors. Cancer 1:441, 1948.

CASE REPORT

Spontaneous hypoglycemic coma in childhood

Richard Aurelius Smith, M.D.

A 25-MONTH-OLD BOY was brought to the emergency room at 11 A.M. on June 24, 1958. A week before, he had struck his forehead falling from a swing. The child had cried but was not knocked unconscious. He soon resumed normal activities.

For 2 days prior to admission, the patient had been anorexic; on the evening before, he refused to eat supper and was spanked severely and put to bed. The next morning he appeared limp, spoke incoherently, and refused to stand up or walk. An attempt was made to feed him breakfast, but he began to vomit and at 8 A.M. became totally unresponsive. The patient's eyes seemed to be pointed downward. Fine twitching movements of his extremities were noted about every fifteen minutes but no major seizures.

On examination, the child was semicomatose and had a contusion over the right forehead and multiple contusions on the lower extremities. Pulse was 100. No nuchal rigidity was found. Intermittent gnashing of the teeth and fine clonic movements of the upper extremities were observed, but, otherwise, no spontaneous motion occurred. The patient's extremities responded only slightly to painful stimuli. His eyes varied from a straight to a convergent position; pupils were pinpoint but dilated on stimulation. Corneal reflexes were present, but blinking reflexes were not. Muscle tone fluctuated between hypertonicity and flaccidity. Reflexes were symmetrically hyperactive with bilateral Babinski signs. Abdominal reflexes were absent.

Roentgenograms of the skull and chest were normal. Hemoglobin was 13 gm., white count, 6,000. Urinalysis was normal, with reaction of 5.5 and specific gravity of 1.018. Lumbar puncture yielded clear, colorless fluid under an opening pressure of 75; no cells were found. Pandy reaction was negative; protein was 21 mg. per cent. The 5-tube semiquantitative sugar test revealed only a trace of sugar in the fifth tube. With this information, blood sugar was immediately obtained and was reported as 8 mg. per cent. Blood urea nitrogen was 24 mg. per cent, calcium, 9.9 mg. per cent.

At 2 P.M. the child was given 20 cc. of 50% glucose intravenously. Response was dramatic. The patient began to cry and fight—dislodging the needle. He appeared alert and, after transient vomiting, was able to take fluids orally. Transferred to the pediatric service, the patient seemed normal during the remainder of his stay in the hospital. A glucose tolerance test revealed a flat curve. After twelve hours of fasting, blood sugar was 53 mg. per cent and after fourteen hours, 19 mg. per cent. At this time, he was weak, lethargic, and unable to stand. On July 4, 1958, the patient was discharged as asymptomatic on a high protein, frequent-feeding diet.

DISCUSSION

Spontaneous hypoglycemia as a cause of convulsions in children was first described by Ross and Josephs in 1924[1] and further by Josephs in 1926[2] and 1929,[3] following Harris' postulation of hyperinsulinism in 1924.[4] In 1932, Elias and Turner[5] recognized that coma might occur without convulsions. Many reports followed.[6-10] More recently, interest has been rekindled by McQuarrie,[11-14] who has pointed out that the condition is not rare. Others have reported similar experiences.[15-18] In most patients, the cause remains obscure.

From the Department of Surgery, Section of Neurosurgery, University of Michigan Hospital, Ann Arbor.

Pancreatic hyperplasia or neoplasm is rarely found in infants or young children; other less common causes of hypoglycemia which should be considered are pituitary and adrenal insufficiency, hypothyroidism, von Gierke's disease, hepatic disease, and galactosemia.[14]

Symptoms are most frequent before the age of 2 and rare after the age of 5 and tend to be intermittent in severity—subsiding as the child grows older. A familial tendency has been noted.[14] In a typical instance, a previously well infant or child, who for some reason—illness, excitement, or punishment—has not eaten properly and perhaps has been unusually active as well, is found to be limp. Characteristically, this happens in the early morning. Vomiting often occurs. The child may be irritable, with twitching, tremors, or jerks of the face and extremities. Pallor and a cold clammy sweat may be seen. Peculiar, rolling movements of the eyes, intermittent strabismus, or a staring expression may be noted. Convulsions are common and may be the initial symptom; however, convulsions may not occur. Coma may eventually follow and, in extreme cases, is sometimes prolonged even after restoration of normal blood sugar. Examination may suggest diffuse cerebral or brain stem disease, as in the patient reported here. Diagnosis of hypoglycemia may be suspected by finding low sugar content in sterile spinal fluid and confirmed by a low blood sugar.[19]

McQuarrie has emphasized the therapeutic aspects,[11-14] including well recognized principles of diet and avoidance of fasting.[20,21] In extreme cases, he has obtained excellent results with steroids.

Hypoglycemia must be differentiated from the variety of traumatic, inflammatory, and degenerative conditions with which it is confused. Extreme, prolonged episodes of hypoglycemia may terminate fatally or result in mental retardation, spasticity, or epileptic seizures eventually unrelated to blood sugar levels.[14-16,22-25]

SUMMARY

This case represents a characteristic syndrome in children. Emphasis is made on the value of spinal fluid and blood sugar determinations as an integral part of spinal fluid study in the elucidation of coma or convulsions of obscure origin. Previous episodes of trauma, so frequent in children, should not lead one to overlook other causes.

REFERENCES

1. Ross, S. G., and Josephs, H. W.: Metabolism of recurrent vomiting. Am. J. Dis. Child. 28:447, 1924.
2. Josephs, H.: Fasting as cause of convulsions. Am. J. Dis. Child. 31:169, 1926.
3. Josephs, H.: Spontaneous hypoglycemia in childhood. Am. J. Dis. Child. 38:746, 1929.
4. Harris, S.: Hyperinsulinism and dysinsulinism. J.A.M.A. 83:729, 1924.
5. Elias, H. L., and Turner, R.: Spontaneous hypoglycemic shock in children. J.A.M.A. 98:2198, 1932.
6. Carr, A. D.: Neurologic syndromes associated with hypoglycemia. J.A.M.A. 97:1850, 1931.
7. Kramer, B., Grayzel, H. G., and Solomon, C. I.: Chronic hypoglycemia in childhood. J. Pediat. 5:299, 1934.
8. Hartmann, A. F., and Jaudon, J. C.: Hypoglycemia. J. Pediat. 11:1, 1937.
9. Recton, J. M., and Jennings, R. E.: Functional hypoglycemia of childhood, with particular reference to recurrent convulsive manifestations. Am. J. Dis. Child. 53:1021, 1937.
10. Holt, L. E., Jr., and Bridge, E. M.: Hypoglycemia in early life. Nebraska M. J. 30:45, 1945.
11. McQuarrie, I., Bauer, E. G., Ziegler, M. R., and Wright, W. S.: Metabolic and clinical effects of pituitary adrenocorticotropic hormone (ACTH) in spontaneous hypoglycemosis. Bull. Univ. Minnesota Hosp. and Minnesota Med. Found. 21:35, 1949.
12. McQuarrie, I.: Spontaneous Hypoglycemia: Clinical and Metabolic Studies. In: Najjar, V. A.: Carbohydrate Metabolism. A Symposium on the Clinical and Biochemical Aspects of Carbohydrate Utilization in Health and Disease. Baltimore, Johns Hopkins Press, 1952, pp. 76-91.
13. McQuarrie, I.: Idiopathic spontaneously occurring hypoglycemia in infants. Am. J. Dis. Child. 87:399, 1954.
14. McQuarrie, I.: Hypoglycemia in infancy and childhood. Postgrad. Med. 18:287, 1955.
15. Gall, J. C., Jr., and Burke, E. C.: Idiopathic hypoglycemosis. Proc. Staff Meet. Mayo Clin. 30:477, 1955.
16. Heberden, P., and Friedlander, F. C.: Hypoglycaemic coma. Arch. Dis. Childhood 30:372, 1935.
17. Perry, J. C., Bourne, I. B., and Henry, W. L.: Idiopathic hypoglycemia in childhood. J. Nat. M. A. 49:29, 1957.
18. Royer, P.: Les hypoglycemies spontanées de l'enfance. Rev. prat. 7:2875, 1957.
19. Crue, B. L., Marshall, J. M., Shelton, R. M., and Shelden, C. H.: Adenoma of pancreas with hyperinsulinism, associated with low sugar content in spinal fluid. California Med. 83:35, 1955.
20. Conn, J. W.: Diagnosis and management of spontaneous hypoglycemia. J.A.M.A. 134:130, 1947.
21. Conn, J. W.: Dietary management of spontaneous hypoglycemia. J. Am. Dietet. A. 23:108, 1947.
22. Baker, A. B.: Cerebral damage in hypoglycemia. Am. J. Psychiat. 96:109, 1939.
23. Courville, C. B.: Late cerebral changes incident to severe hypoglycemia (insulin shock). Arch. Neurol. & Psychiat. 78:1, 1957.
24. Fahlgren, H., Andersson, B., and Lundmark, C.: Prolonged unconsciousness in connection with an attack of hypoglycemia. Acta med. scandinav. 158:97, 1957.
25. Meyer, A.: Anoxias, Intoxications, and Metabolic Disorders. In: Greenfield, J. G., Neuropathology. London, Edward Arnold, 1958, pp. 245-247.

Clinicopathologic Conference

E. P. Richardson, Jr., M.D., *Section Editor*

Presented by J. Dana Darnley, M.D., and Jose Bebin, M.D.

Case presentation. A 67-year-old woman was admitted to the hospital because of pain in the lower back. She had fallen on a staircase five days before admission and struck the midportion of her back against the corner of a stair. Immediately after the accident, she had severe pain in the lower dorsal and upper lumbar area radiating to the left side. The pain subsided to a dull, steady ache and remained localized in these areas.

The patient was able to walk but found that walking made her pain worse. Nausea and periodic vomiting began three days before admission. The patient had consulted a Christian Scientist practitioner shortly after the accident but had finally sought medical attention when the pain in her back persisted.

Her past health had been good. She had slight diabetes mellitus two years before with increased urinary frequency and polydipsia. However, these symptoms, as well as her glycosuria, were easily controlled by diet. She had also had a mild, flu-like illness the week before her accident. This illness was poorly described as a generalized myalgia with a small temperature elevation and a slight, nonproductive cough. These symptoms were not present at the time of admission to the hospital.

Physical examination. The patient was a well-developed, obese, white female, unable to stand because of back pain; temperature was 98.4° F.; pulse, 80 per minute; blood pressure, 170/100; height, 5 ft.; weight, 140¾ lb. Marked tenderness was noted over the lower dorsal and upper lumbar spine; eyes, including funduscopic examination, were normal. Lungs were clear without rales. The heart had normal sinus rhythm with no murmurs or apparent enlargement. Liver and spleen were not palpable, and there were no abdominal masses or tenderness. Bowel sounds were normal. Neurologic examination revealed no loss of motor power in the upper or lower extremities and no definite sensory changes except for an ill-defined area of hypesthesia in the lateral portion of the left midthigh. Deep tendon reflexes in the upper and lower extremities were present and equal.

Laboratory findings. Hemoglobin was 13 gm.; white blood count, 11,850; polymorphonuclear leukocytes, 81; lymphocytes, 11; monocytes, 8. Urinalysis revealed: specific gravity, 1.025; albumin, 1 plus; Benedict's test, negative; 3 to 4 finely granular casts; 3 to 5 leukocytes; nonprotein nitrogen, 40; fasting blood sugar, 150 mg. per 100 cc.; carbon dioxide, 25.2; chlorine, 91; sodium, 134; potassium, 3.2 mEq. per liter. Roentgenograms of the lumbar and dorsal spine showed no fracture.

Hospital course. On the morning after admission, the patient seemed less clear mentally than before, and a two-hour post cibum blood sugar of 230 mg. per 100 cc. was obtained. She was placed on regular doses of insulin according

From Henry Ford Hospital, Detroit.

to urine sugar determinations. On the evening of the patient's second day in the hospital, she complained of numbness and inability to move her legs. The neurologic examination at that time was as follows:

> The patient appears very ill and extremely weak. Cranial nerves normal. There is apparent generalized weakness of the proximal muscles at the shoulder and the hip. There is generalized areflexia. There is definitely impaired position sense in the left foot and decreased vibratory sense in both feet. The patient has apparently no voluntary bladder or bowel function.

The examining physician's impression was "an advancing, flaccid paraparesis."

A *spinal fluid examination* was done soon after, with the following results: fluid, crystal clear; initial pressure, 200 mm.; normal manometric response; no cells; Pandy's test, 1+; protein, 156 mg. per 100 cc.; Lange's test, 1112211000; no culture.

Laboratory findings on the third hospital day showed: urine: specific gravity, 1.019; albumin, 0; Benedict's test, 0; no casts; fasting blood sugar, 150; nonprotein nitrogen, 30 mg. per 100 cc.; carbon dioxide, 26.1; chlorine, 102; sodium, 124; potassium, 4.8 mEq_l. per liter.

The patient's condition remained the same until the morning of the third hospital day when respiration suddenly ceased. She was given emergency artificial respiration and was placed in a Drinker respirator. In the respirator, she was treated with oxygen, pharyngeal suction, intravenous fluids, and various medications including tetracycline, hydrocortisone, and Levophed. The patient remained semiconscious, made feeble attempts to talk, and seemed able to move both hands. She could move her right leg slightly, but not her left. A specific neurological examination was not possible. The patient continued in this state for approximately twelve hours. Shortly before death, respirations were gasping, and blood pressure was 60/54. The patient was areflexic and had no corneal or pupillary reflexes. She died early on the fourth hospital day.

Discussion

DR. J. DANA DARNLEY: This was an older individual—a 67-year-old woman who had mild diabetes two years before she came in. The two-year interim is a total blank, but we are led to believe that this remained a mild diabetes without insulin therapy and without dietetic treatment. About ten to fourteen days before she came in, she had a flu-like illness with low-grade fever, slight nonproductive cough, and generalized aching of the muscles or malaise. We presume this lasted four to five days; at least, it was gone by the time she got to the hospital. As an immediate sequel of a back injury five days before admission, she developed back pain at the level of the injury which radiated to the left flank. Three days before admission, and two days after the pain had begun and stayed, the patient became nauseated and vomited several times a day.

The flu-like illness, plus nausea and vomiting, indicate systemic lurkings behind the mere fact that the patient fell down stairs and hurt her back. On the day of admission, her general physical status was actually not very far from normal—the only things worth commenting on were a degree of hypertension (170/100), inability to stand because of back pain, spine tenderness over the low dorsal and lumbosacral spine, and an ill-defined hypesthesia over the lateral portion of the left midthigh. This would correspond to the L2 dermatome on the left side and would lend a little more credence to our accepting the back pain radiating into the left flank as possibly root pain; that is, the level of pain and the distribution of hypesthesia are consistent with an L2 root lesion.

The laboratory studies help us out to the extent of a leukocytosis of 11,800 with 81% polymorphonuclears, which again lends support to the idea of underlying systemic illness. The patient's serum electrolytes were not far from normal range. I think the potassium at that time was slightly low. The nonprotein nitrogen was a little up and the fasting blood sugar was 150—so that her diabetes was not perfectly controlled, although she had no glycosuria.

Now, three and one-half days after being in this fairly normal state, the patient died.

The day after admission, the patient was noted to be "not quite so clear mentally" and a two-hour post cibum blood sugar test was 230 mg. per cent. This is elevated, of course, but I should think it does not satisfactorily

explain the slight degree of mental confusion. At any rate, she was then put on insulin around the clock, guided by the degree of glycosuria in specimens taken four times a day.

On the evening of the second day, she experienced the beginnings of what proved to be her total undoing thirty-six hours later—the apparently rapid onset of numbness and weakness in both legs. This was her only complaint at the time, but, on examination by a neurosurgical consultant, the patient was found to have weakness of the upper, as well as the lower, extremities—primarily in the proximal muscle groups—in other words, in the shoulder girdle and pelvic girdle muscles. Generalized flaccidity and areflexia occurred plus some changes in position and vibration sense in both feet. Apparently, no other sensory modalities were involved. The patient, at this time, had no voluntary control of the bladder or bowel, which indicates interference with sacral outflow. She showed no evidence of cranial neuropathy.

The patient was described as looking "very ill and extremely weak," in definite contrast to the intern's description of her general appearance on admission. The consultant, I am sure, was misquoted in the report—his findings indicated an acute, flaccid quadriparesis, not paraparesis. Note the sensory deficits lagged behind the motor and reflex deficits.

That night, the cerebrospinal fluid showed an initial pressure of 200, which is upper limit of normal in a 5-ft. woman weighing 140 lb. The Queckenstedt—a very important test in this setting—was reported to be negative. The spinal fluid protein was 156 mg. per cent and the cell count was 0. This, of course, is the classic albuminocytologic dissociation — the gross discrepancy between protein, highly elevated, and cell count, very normal—first described in 1916 in an article by Guillain, Barré, and Strohl.[1-3]

From this point on, the patient's course went rapidly downhill—from leg symptoms and signs, to arm signs, to cessation of respiration in about twelve hours. In another twenty-four hours, the patient was dead.

I think the description of the terminal phase of the last day really does not add much to the picture. There are comments that she could move her hands, that she moved her right leg a little more than her left, and that she terminally lost corneal and pupillary reflexes; but I feel that she had by that time run out of so much function, respiratory-wise and otherwise, that these clinical comments do not give us the clear-cut brain stem localization that they would have in an intact person. This patient was far from intact at that point.

In short, this woman died fourteen to eighteen days after her flu-like illness. She died nine days after the sudden onset of back pain. She died thirty-six hours after the abrupt onset of flaccid quadriparesis primarily involving the proximal muscles, and of total areflexia, and relative minor sensory deficits; she had no fever, a little leukocytosis, a classic albuminocytologic dissociation, and a negative Queckenstedt test. In this, using the adjective "classic" is permissible, but we must recognize that this so-called albuminocytologic dissociation occurs in cord compression syndromes, too, of course, which may often have a normal cell count with a very high protein count so that negative Queckenstedt is very important information.

Well, this, I hope, clarifies the course of this lady's illness for us. We haven't yet drawn any definite conclusions, but, looking back on this, if we could just turn aside a couple of "herrings"—I hope of multicolor—this would be a reasonably clear-cut situation. In other words, this very abrupt onset of what in a short time became a flaccid, areflexic, quadriparesis with relatively minor sensory symptoms and signs and with albuminocytologic dissociation, is really a classic picture of the now often-combined terms of Landry-Guillain-Barré syndrome.

Now, before we try to confirm this, I would like to digress for a moment and discuss the herrings, if they are herrings! First of all, the diabetes. Could this lady's diabetes have played a role in this final illness? We are told that it was mild from the beginning. The electrolytic studies would not lead us to think that it was much more than that now. It looks to me as if it wasn't very far out of control, and I don't believe that it had anything to do with this terminal illness. I looked up the motor neuron complications in a monograph of diabetic neuropathies, and this just is not reported. We just don't see acute ascending paralysis of this sort in diabetic neuropathy.

Second—and this is the herring that bothers me—the patient came into the hospital because of her back pain and she got her back pain when she fell down stairs. Well, though it looks as if trauma is rearing its ugly head, I choose to think of this as a herring. Be that as it may, when we think of back injuries, we think of fracture-dislocations, but we know from roentgenograms that this lady did not fracture her low dorsal or lumbosacral spine. Conceivably, she could have produced a traumatic subarachnoid hemorrhage, but the cerebrospinal fluid showed neither gross nor microscopic blood; she could have produced, I suppose, a hematomyelia, but this, like any other intramedullary cord lesion, should, even in the relatively brief time that she lived after the accident, have produced some long-tract sensory interruptions; of these we have none. I suppose disk disease—a thoracic disk suddenly popping out and producing cord compression—might be considered, but again we have no long-tract sensory signs, and we would like to see the extensor toe signs coming through, but they didn't. Furthermore, the Queckenstedt test was negative. With her flu-like illness, leukocytosis (admittedly not very high), back pain and tenderness, and acute ascending neurologic deficits, I suppose even epidural abscess might be remotely considered; but this, although I remember a case that fooled me by its insidiousness, for the most part features high fever, definite signs of sepsis, and abundant cord compression signs with long-tract interruptions, both efferent and afferent. So, for the purposes of the discussion at least, I will dismiss the diabetes and the back trauma as factors, despite the prominence of the latter in the history.

Getting back to the Landry-Guillain-Barré syndrome, this is classically described, as you all know, as a symmetric, flaccid quadriparesis or quadriplegia which often affects the proximal more than the distal muscle groups with areflexia and is commonly found with albuminocytologic dissociation and often with cranial neuropathy. Sometimes the disease occurs in this acute ascending fashion and causes death in a few days. In 40 of 50 fatal cases that Haymaker and Kernohan reported, a previous upper respiratory or gastrointestinal tract infection had occurred.[2] Our patient had a flu-like illness ten to fourteen days before this catastrophic ending. The nausea and vomiting, and the pain—even pain of sudden onset—would be much in keeping with the Landry-Guillain-Barré syndrome. The early hypesthesia is consistent, as is the polymorphonuclear leukocytosis, although Haymaker and Kernohan report a fair number with lymphocytosis as well. Sudden death is not out of keeping with the syndrome, and the normal general physical examination is not surprising. Death in respiratory failure is the common way out, and this is the way our patient went.

In summary, I think this is a very reasonable diagnosis—namely, the Landry-Guillain-Barré syndrome. In connection with their work on this syndrome, Haymaker and Kernohan found 2 cases of infectious mononucleosis underlying this syndrome and, from the histologic findings in the spleen, suspected infectious mononucleosis as the etiology in 6 others; so that this, too, might be considered. However, I think it is unlikely in an older woman. Incidentally, at this time nobody knows what causes these Landry-Guillain-Barré syndromes; they are still popularly attributed to a neurotropic virus, but this is unproved. The pathology is primarily in the root, a polyradiculoneuropathy, with relatively minor changes in the cerebrospinal axis.

Now, in any acute ascending paralysis, from which this patient apparently died within thirty-six hours, there are a few other etiologic situations that might be considered. First of all, according to Kinnier Wilson, practically any infectious disease—poliomyelitis, childhood exanthemata, typhoid, rabies, and so on—can be followed by an acute ascending paralysis of, as he calls it, Landry's type. I think we can pretty well skip these factors here, since, from our report, at least, we have no indication of any of these specific infectious diseases. Some of the heavy metal intoxications—lead, arsenic, mercury—instead of causing their much more typical peripheral neuropathies without the dramatic coloring of this situation, may rarely produce an acute ascending paralysis. Here, too, from the report we have no suggestion that this lady has been exposed to any of the heavy metals.

We turn then to consideration of a couple of metabolic points of some interest. First of all, there is the entity of acute intermittent

porphyria. This is something that we see, or, at least, detect, rarely here, though Dr. Peters of Madison is now reporting on around 43 or 45 cases in the last few years.[5] The fact is that females do predominate, but the usual age group of such patients is between the third and fifth decades, so that our patient is out of the usual range—at least on this score. Pain, especially abdominal pain, but occasionally back or flank pain, is characteristic of porphyria, and our patient, a Christian Scientist, presumably had excruciating pain, since she came into the hospital for treatment. Aberrations of mentation or personality are common with porphyria, but our patient's only nod in that direction was her apparent slight confusion the day after admission. Finally, the Landry paralysis or the acute ascending paralysis is not unheard of in acute intermittent porphyria. The spinal fluid protein is, however, usually only slightly elevated, and our patient had a very high 156. For several of the above reasons, this disease would appear to me to be an unlikely, although interesting, possibility.

The serum potassium level, whether abnormally high or low, has been incriminated in producing the clinical picture of acute ascending paralysis; hyperkalemia, in fact, has been reported as producing the most rapid evolution of Landry's ascending paralysis—something that goes "from lower extremities to bulbar outflow" in a matter of a couple of hours! This critical situation is usually reversible (if the diagnosis is made) with sodium chloride therapy. It's worth noting, at least in 2 such cases reported from Peter Bent Brigham about 10 years ago, that the spinal-fluid protein was well within normal limits. The hyperkalemia is secondary usually to salt-losing nephritis or diabetic coma. As we stated before, our patient did not appear to be in anything even remotely resembling diabetic coma and, although I'll admit I know little about salt-losing nephritis, from the electrolytic picture, at least, it looks as if the chemical budget was pretty well balanced; and, furthermore, the urine didn't point too strongly to nephritis.

On the other side of the coin, serum potassium, when too low, can produce something simulating the same syndrome. Hypokalemia may result from prolonged vomiting; now we know that our patient was nauseated and vomited for three days episodically. On the other hand, the actual serum potassium level was initially only 3.2 (just below the normal), but had reached a normal 4.8 when she was really critically ill, so I guess we can rule that out. Hypokalemia may also occur with uremia or in the course of treatment of diabetic coma, but neither applies here.

Finally, a few of us here have had some enlightening experiences lately with the neurologic complications of lymphomas and we have noted some strange happenings in both the central and peripheral nervous system in this disease, so I was very interested to see a report in the July 1955 issue of *Lancet* which seemed relevant to the case in point.[4] The case reported did indeed meet the clinical criteria for the diagnosis of Guillain-Barré syndrome, even to the cerebrospinal fluid protein of 275 mg. per cent with only 14 lymphocytes. The patient died after a twelve-week illness and at autopsy had reticulum-cell sarcoma involving one cerebral hemisphere, the midbrain, meninges, and many roots in the thoracic cord. One wonders if the systemic manifestations mentioned previously—namely, the flu-like illness, the nausea and vomiting, the pains and paresthesia, the polymorphonuclear leukocytosis, and so on—might not shore up the remote possibility of lymphoma here. But the same items shore up much better the prototype of all acute ascending paralysis, the Landry-Guillain-Barré syndrome. It would be most unusual, I should think, for a lymphoma or a related tumor to produce death in an acute ascending paralysis in such a short time.

In summary, then, I have mentioned these other possibilities so that, when Dr. Bebin shows what really happened—and I am as anxious to find out as anybody—they will at least have been mentioned. However, I would favor the Landry-Guillain-Barré syndrome of undetermined etiology.

Pathologic Discussion

DR. JOSE BEBIN: The autopsy was performed three and one-half hours after death. No unusual findings were noted on gross examination. The *heart* weighed 420 gm. Some hemorrhagic discoloration was noted at the apex of the left ventricle, but no areas of softening

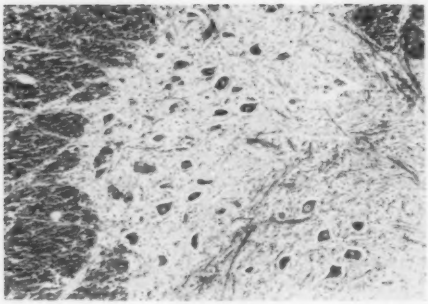
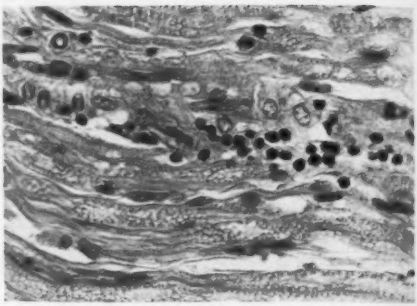


Figure 1



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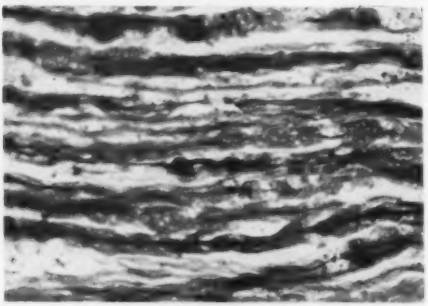

Figure 3

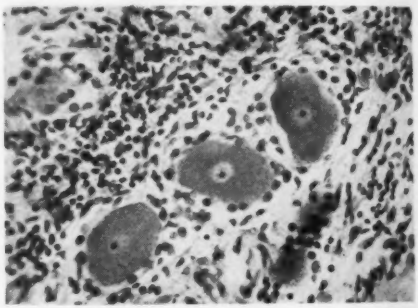

Figure 4

were encountered. On microscopic examination, the left ventricular myocardium revealed areas of considerable hyperemia with abundant neutrophilic infiltration between myocardial fibers, slight loss of muscular striations, and proliferation of capillaries. The coronary arteries revealed eccentric atheromatous changes in their intima and media tunics, reducing considerably the lumen of the vessel but not occluding it. The changes in the myocardium are interpreted as early manifestations of a recent myocardial infarct without coronary occlusion.

The right *lung* weighed 530 gm., and the left, 310 gm. Microscopic examination revealed generalized congestion and focal areas of pulmonary edema. The bronchi were filled with an inflammatory exudate consisting chiefly of polymorphonuclear cells, debris, focal collections of bacteria, and partially digested fragments of vegetable. The adjacent alveoli were also filled with similar exudate. Focal areas of atelectasis were seen here and there. Numerous, small (0.4 x 0.3 x 0.3 cm.), yellow nodules were present in the capsular surface of the *spleen*. Microscopic examination revealed congestion of the red pulp. In many of the malpighian bodies there was a hyalin degeneration. The *liver* weighed 1,520 gm. and showed a yellow, mottled appearance throughout. Microscopic examination showed a diffuse, rather severe fatty infiltration throughout the parenchyma.

Extreme congestion was also found in all the other organs. No gross or microscopic abnormalities were found in the gastrointestinal tract, kidneys, pancreas, and glandular system.

Central nervous system. The brain weighed 1,220 gm. It appeared to be congested. The leptomeninges were slightly thickened and their vessels moderately engorged. The circle of Willis showed marked arteriosclerotic changes. Coronal sections of the brain had moderate edema and congestion throughout. The ven-

tricles were symmetric and normal in size. Microscopic examination of the brain showed the following: meninges moderately thickened and fibrotic and meningeal vessels congested. The cerebral cortex and white matter showed moderate edema and congestion throughout. There were occasional areas of falling out of neurons, and a few small perivascular hemorrhages. The basal ganglia and thalamus had similar features. The blood vessels in these regions showed severe arteriosclerosis. The choroid plexuses were extremely congested and contained numerous calcific deposits. The brain stem—midbrain, pons, and medulla—and the cerebellum were moderately congested and edematous.

Spinal cord. The spinal cord was removed by the anterior approach. The cord itself appeared normal, except for considerable congestion and thickening of the meninges. Microscopic examination of the spinal cord at different levels (cervical, thoracic, lumbar, and sacral) by different staining technics showed the meninges to be moderately thickened and fibrotic and the vessels extremely engorged. The gray and white matter of the cord showed congestion and edema—the congestion greater in the gray, the edema predominating in the peripheral white matter. The neurons of the anterior and posterior horns were normal, and there was only an occasional ganglion cell with some central chromatolysis (Fig. 1). The myelin sheaths were well stained with the Klüver technic. Abundant corpora amylacea were found in the marginal zone.

Peripheral nervous system. Spinal ganglia and nerves from different levels were examined by hematoxylin and eosin stain, Nissl stain, silver technics, and flaming red stain for lipids. The nerves, particularly in their proximal segment to the ganglia and the cord, showed edema and congestion. The myelin sheaths appeared edematous and early degeneration of the myelin had begun in the fat stain. The axons were edematous, tortuous, and irregular and, in some areas, showed fragmentation and distortion (silver stain). Within the nerve bundles, moderate lymphocytic infiltration was found, and there seemed to be some proliferation of the Schwann cells (Figs. 2 and 3).

The ganglia showed edema and congestion and moderate lymphocytic infiltration diffusely arranged or in clusters (Fig. 4). The ganglion cells appeared to be normal. Few of them showed increased amount of lipochrome pigment in their cytoplasm.

Summary

The anatomic examination of the central and peripheral nervous systems of this patient revealed [1] significant lesions in the nerves, ganglia, and roots and [2] anatomic integrity of the central nervous system. The lesions in the nerves, ganglia, and roots were mainly an interstitial lymphocytic infiltration, edema and congestion, and early myelin and axonal degeneration. In contrast, the neurons of the spinal gray were normal.

These pathologic changes in the nervous system of this interesting patient are compatible with the diagnosis of Guillain-Barré syndrome—acute infectious polyneuritis. The cause of death could also be attributed to an acute myocardial infarction of approximately twenty-four hours duration without coronary occlusion and aspiration type bronchopneumonia.

REFERENCES

1. Guillain, G., Barre, J. A., and Strohl, A.: Sur un syndrome de radiculo-névrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire. Bull. et mém. Soc. méd. Hôp. Paris 40:1462, 1916.
2. Haymaker, W., and Kernohan, J. W.: Landry-Guillain-Barré syndrome; clinicopathologic report of 50 fatal cases and a critique of the literature. Medicine 28:59, 1949.
3. Guillain, G.: Considerations sur le syndrome de Guillain et Barré. Ann. de méd. 54:81, 1953.
4. Allison, R. S., and Gordon, D. S.: Reticulosis of the nervous system simulating acute infectious polyneuritis. Lancet 2:120, 1955.
5. Peters, H. A., Eichman, P. L., and Reese, H. H.: Therapy of acute, chronic and mixed hepatic porphyria patients with chelating agents. Neurology 8: 621, 1958.

Neurology

BOOK REVIEWS

The Waking Brain

by H. W. Magoun, 138 pp., ill., Charles C Thomas, Springfield, Ill., 1958. $4.75

This book—the most recent Thomas W. Salmon lecture—is a fortunate contribution and brings together in brief, yet well organized, form the research results of the author and his associates.

Taking up the gauntlet thrown down by Cajal that specificity of neuronal connection is the primary object for demonstration in the nervous system, Magoun begins by postulating "a major non-specific or transactional mechanism in the brain paralleling the specific sensory and motor systems of classical neurology and richly interconnected with them."

How this diffuse coordinating mechanism influences the spinal cord, the diencephalon with its pituitary connections, the rhinencephalon, the neocortex, and the basal ganglia, is the question proposed for answer.

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The author reviews and clarifies studies on the influence of the reticular system on the hypothalamus and neuroendocrine mechanism. Evidence is presented that excitation of the reticular system stimulates hypothalamico-pituitary activity and consequent ACTH elaboration increases and regulates secretion of gastric hydrochloric acid and influences thyrotropic and gonadotropic hormones.

A résumé of the experimental data on the effect of the reticular core and the rhinencephalic system on emotions is presented; here the relationship to the reticular system is often a remote or an assumed one.

The neuroanatomist will miss structural identification of the reticular system and will want some description of its boundaries and a note about the morphology of its cellular elements.

This book is an important one and will have a wide circulation. It will be appreciated best by those who know the series of papers on which it is based. Since the book compresses an astounding amount of data, the reader may be reminded that, in spite of gracefully light comment here and there, it can hardly be read without a full measure of close attention. For this effort, the reader will be rewarded with a new and stimulating approach to neural mechanisms.

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Zier, A. and Doshay, L. J.: Procyclidine Hydrochloride (Kemadrin) Treatment of Parkinsonism in 108 Patients, Neurology (July) 1957.

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Lerner, P. F.: Kemadrin, a New Drug for Treatment of Parkinsonian Disease, J. Nerv. & Ment. Dis. 123:79 (Jan.) 1956.

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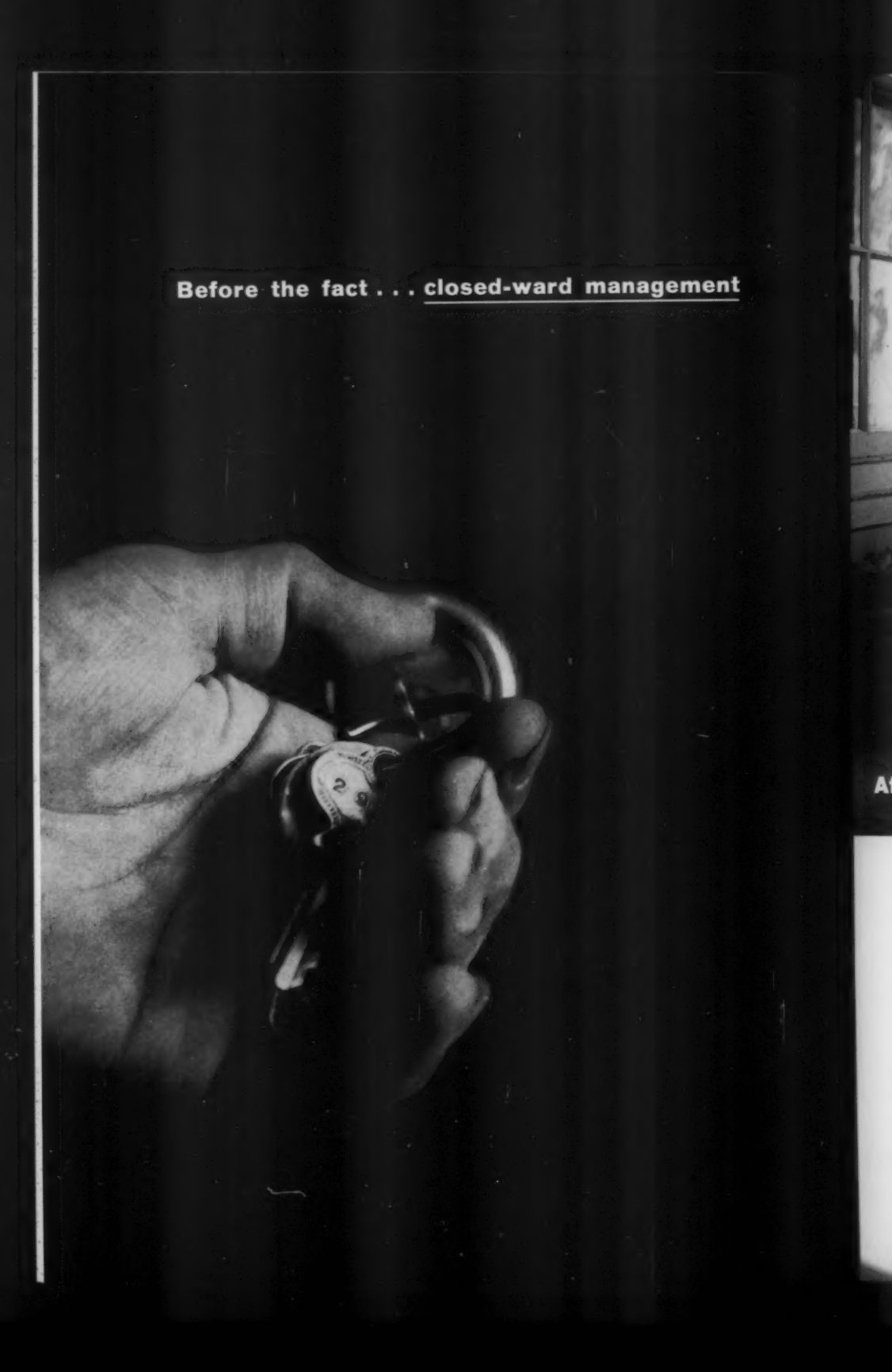
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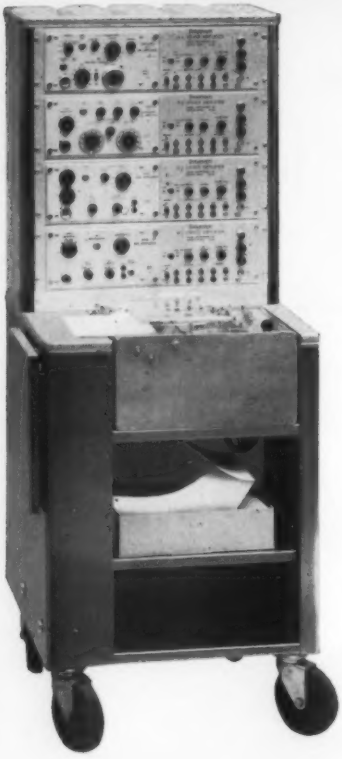

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APRIL 1959

Second International Symposium on Myasthenia Gravis To Be Held in Los Angeles

In conjunction with the eleventh annual AAN meeting (April 13-18, 1959) the Second International Symposium on Myasthenia Gravis will be held at the Statler-Hilton Hotel, Los Angeles. The Symposium is sponsored jointly by the Myasthenia Gravis Foundation and the National Institute of Neurological Diseases and Blindness. The aims of the Symposium are to bring up to date our present knowledge in the field of myasthenia gravis; indicate new paths of fruitful research for the next five years; and serve as a general guide of programming in this field. Among the distinguished foreigners to participate in the sessions will be N. I. Grashchenkov, who is now Assistant Director-General of the World Health Organization. The Program Director of the Symposium is Kermit E. Osserman, 4 East 89th Street, New York City 28.

American Board To Certify in Child Psychiatry

The American Board of Psychiatry and Neurology announces that it is now undertaking subspecialty certification in child psychiatry for those child psychiatrists who meet the required standards. Further information may be obtained from Dr. David A. Boyd, Jr., Secretary-Treasurer, American Board of Psychiatry and Neurology, Inc., 102-110 Second Avenue, S.W., Rochester, Minn.

Beach and Wilson Win ARNMD Awards

At its December 13, 1958, executive sessions the Association for Research in Nervous and Mental Disease announces its first annual awards for individual scientific contributions. In psychiatry, an award of $1,000 was made to Frank Ambrose Beach, Ph.D., professor of psychology at the University of California (Berkeley) for his work in demonstrating the fruitfulness of the psychobiologic approach to the study of behavior. In neurology an award of $1,000 was made to Irwin B. Wilson, M.D., associate professor of biochemistry at Columbia University for his work in explaining the action of toxic gases on the nervous system. The presentations were made by H. Houston Merritt, Chairman of the ARNMD Awards Committee....The 1959 officers of the ARNMD are Lawrence C. Kolb, President and Chairman of the Commission; Richard L. Masland and Robert E. Cooke, Vice-Presidents. Rollo J. Masselink continues as Secretary-Treasurer. The 1960 meeting of the ARNMD will be at

New York's Hotel Roosevelt (December 11-12); the topic for consideration is mental retardation.

Sir Francis Walshe to Give Bishop Lecture at Washington University William M. Landau, associate professor of neurology, announces that Sir Francis Walshe of the National Hospital, Queen Square, London, will deliver the George H. Bishop Lecture in Experimental Neurology at the annual Washington University neurology and neurosurgery alumni conference on Friday evening, April 10, 1959. The day sessions of April 10 will be devoted to the presentation of papers by the alumni of this group. Sir Francis Walshe who is now a visiting professor of neurology at Washington University will tour other neurologic centers throughout the country and will attend the annual meeting of the American Academy of Neurology in Los Angeles.

Neurological Institute Planned for Arizona Already under way are plans for the construction in Phoenix of a new neurological institute, to be known as the Barrow Neurological Institute. The Institute is to be constructed as a wing of St. Joseph's Hospital of the same city. The project was made possible by a donation from Mr. Charles A. Barrow and family, which when matched with Federal grants is to exceed $1 million. The project is a memorial to William E. Barrow, father of Charles A. Barrow....The activities of the new Institute represent an extension of the Department of Neurology and Neurological Surgery at St. Joseph's Hospital, headed by Dr. John R. Green, who has been named director of the new Institute. According to Dr. Green, the Barrow Neurological Institute will serve a threefold purpose: (1) as a center specializing in the diagnosis and treatment of hospitalized neurologic patients; (2) as a center for basic research in the etiology and therapy of nervous and mental diseases; and (3) as a center for training neurologists, neurosurgeons, and research workers in this field.

Dutch Research Institute To Celebrate 50th Anniversary To celebrate its 50th Anniversary, the Dutch Central Institute for Brain Research is organizing an international meeting of 50 specially invited neurologic scientists to discuss the problem of the function and structure of the cerebral cortex. The sessions will be held in the seat of the Royal Dutch Academy of Sciences, a famous seventeenth century building called the Trippenhuis in Amsterdam (September 22-25, 1959). The program includes daily opening addresses by Professor F. Bremer (Brussels) on "The Interpretation of Electrical Potentials of the Cerebral Cortex"; Professor H. Waelsch (New York) on "Trends in Neurochemistry as Related to the Cerebral Cortex"; and by Professor and Dr. S. T. Bok, director of the Dutch Institute on "Quantitative

Analysis of the Morphological Elements of the Cerebral Cortex." These addresses will be followed by papers on special topics. The translations will eventually be embodied in a monograph. Since the congress is the jubilee meeting of a state institute, no fees for registration or excursions will be charged to the invited participants. The state will offer a dinner in the "Muiderslot," a medieval castle in which much of the old Dutch atmosphere and culture has been preserved....This meeting is also dedicated to the memory of C. U. Ariëns Kappers, the first director of the Dutch Central Institute for Brain Research, which has played an important role in the development of basic neurology both in Western Europe and the United States.

van Bogaert To Direct International Encephalitis Symposium

Doctor Ludo van Bogaert, president of the World Federation of Neurology, will direct an international symposium on the neuropathology of the encephalitides at the Institut Bunge in Antwerp (May 10-14). The symposium is being sponsored by the World Federation of Neurology, the Centre Interuniversitaire de Recherches Neuropathologiques, and the National Institute of Neurological Diseases and Blindness....The purpose is to develop uniform classification criteria in the pathology of the encephalitides, often described in different localities under different names, and to identify histopathologic patterns of the encephalitides of known viral identity and to study from a neuropathologic point of view the value of presumptive diagnostic evidence in the absence of viral identification. Sets of relevant neuropathologic sections prepared by leading neuropathologists in different countries have been distributed to the conferees in advance so that they may study them before the symposium. Similar sets of slides will be on display during the sessions. While the neuropathology of the encephalitides will make up the central core of the symposium, there also will be a one-day session on EEG correlates under J. Radermecker and a day's sessions on electrophoretic studies of biological fluids in encephalitis under Dr. A. Lowenthal. The official languages of the symposium are French, English, and German....All communications should be addressed to Dr. Ludo van Bogaert, 59, rue Phillipe Williot, Berchem-Anvers, Belgium.

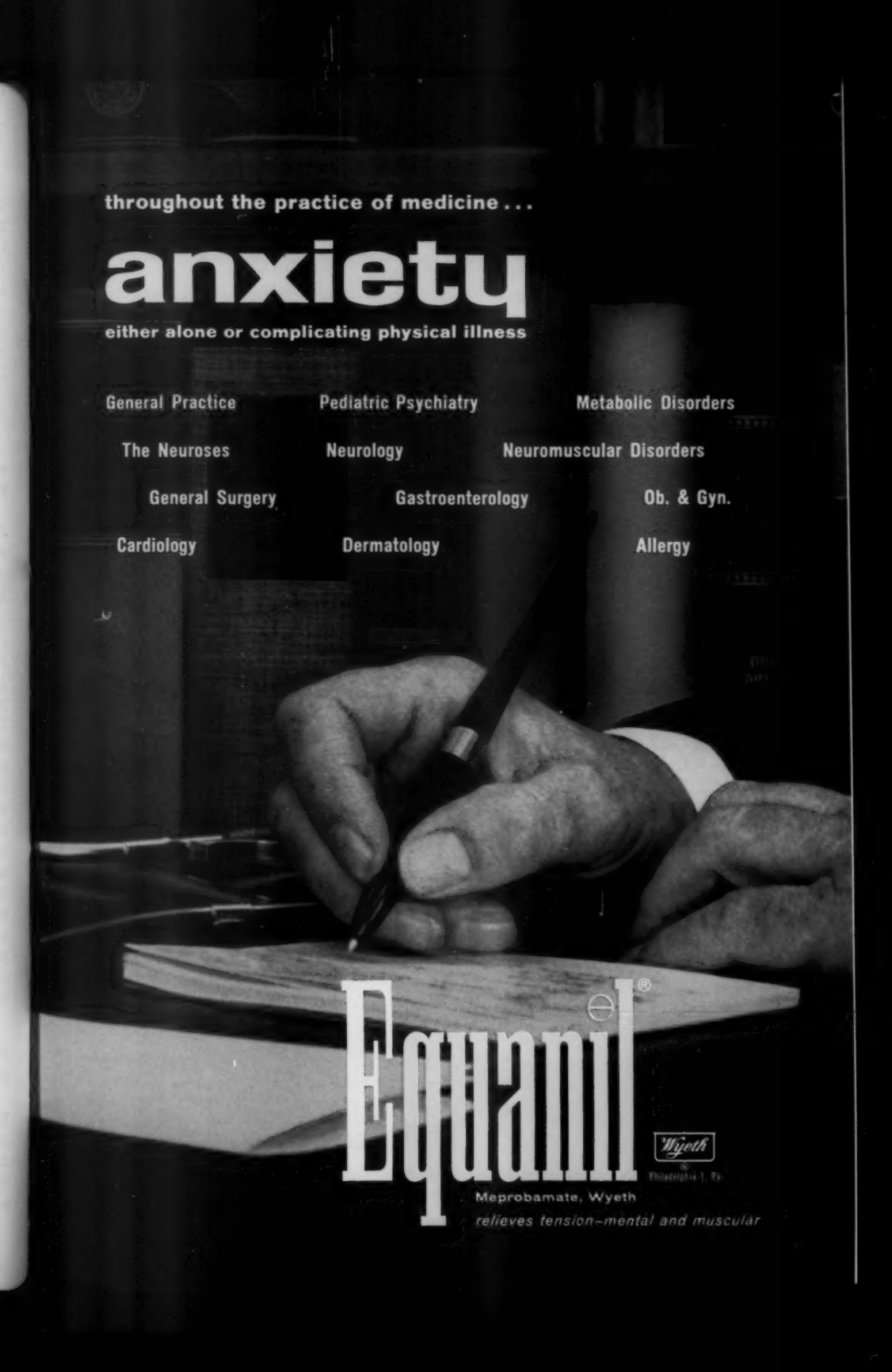
Poch Elected President of Argentina Neurological Society

On December 19, 1958, Dr. Gustavo Francisco Poch of Buenos Aires was elected President of the Argentina Neurological Society for 1959 and 1960. Other officers elected were: Julio C. Ortiz de Zárate, Vice-President; Eduardo F. Soto, Secretary; Angel Monti (Córdoba), Undersecretary; and Héctor A. Figini, Treasurer; the trustees of the Society are Drs. Aranovich, Garrote, Insausti, Levit (Rosario) and Pereyra-Käfer. The

Argentina Neurological Society will hold its first Neurological Congress in Buenos Aires, November 5-7, 1959.

Briefs The Max-Planck Institute for Brain Research in Cologne-Merheim inaugurated a new building for their Division of General Neurology (January 30, 1959)....Professor Dr. N. I. Grashchenkov has joined the Editorial Board of the new journal, EXPERIMENTAL NEUROLOGY, edited by William F. Windle and published by the Academic Press of New York. Grashchenkov, a neurologist and neuropathologist of international renown, is now Assistant Director-General of the World Health Organization....Francis C. Grant, Emeritus Professor of Neurological Surgery, University of Pennsylvania School of Medicine, will deliver the annual Charles A. Elsberg Lecture on Tuesday, May 19, 1959, at 8:30 p.m. at the New York Academy of Medicine. The subject of his lecture is "Trigeminal Neuralgia"....Charles M. Poser, Assistant Professor of Medicine and Head of the Section of Experimental Neurology, University of Kansas Medical Center, has been granted a year of absence to serve as Medical Executive Officer of the World Federation of Neurology (see March 1959 Newsletter).

Peter Bailey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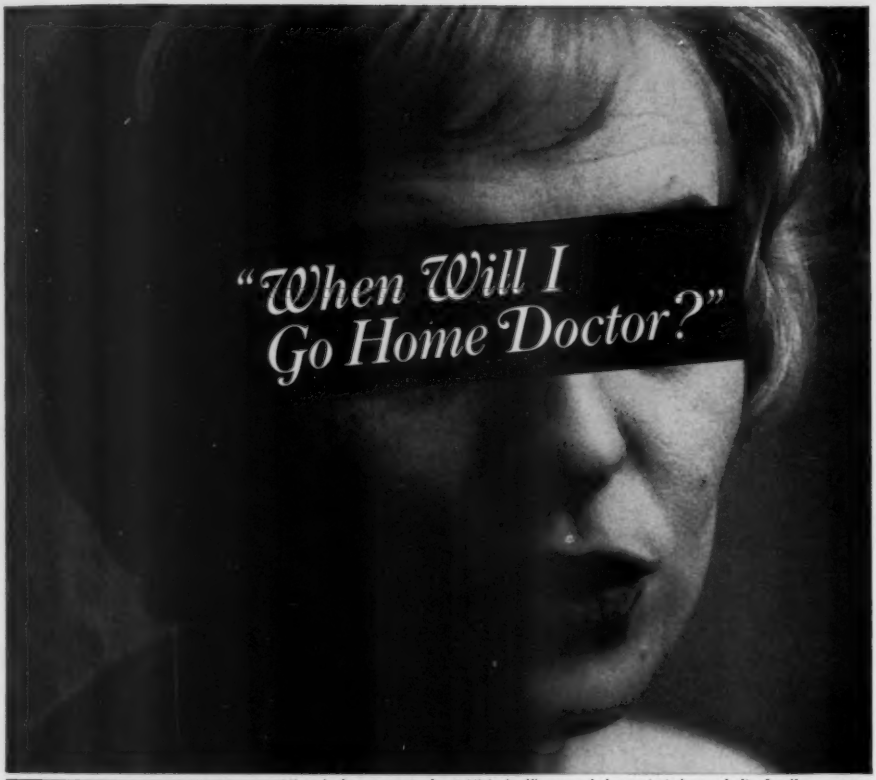

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1 Goldman, D.: Am. J. M. Sc. 235:67 (Jan.) 1958. 2. Morehouse, W. G., and Freed, J. E.: Monographs on Therapy 3:32 (May) 1958. 3. Leger, V.: Union Med Canada 87:831 (July) 1958.
4 Bruckman, N. S.; Saunders, J. C., and Kline, N. S.: Monographs on Therapy 3:24 (May) 1958.

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References: 1. Barsa, J. A.: Am. J. Psychiat. 115:79, July 1958. 2. Graffagnino, P. N., Friel, P. B. and Zeller, W. W.: Connecticut M. J. 21:1047, Dec. 1957. 3. Hollister, L. E., Elkins, H., Hiler, E. G. and St. Pierre, R.: Ann. New York Acad. Sc. 67:789, May 9, 1957. 4. Pennington, V. M.: Am. J. Psychiat. 114:257, Sept. 1957. 5. Tucker, K. and Wilensky, H.: Am. J. Psychiat. 113:698, Feb. 1957.

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1. Holowach, J., and Thurston, D. L.: J. Pediat. 53:160, 1958. Acetazolamide Lederle

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